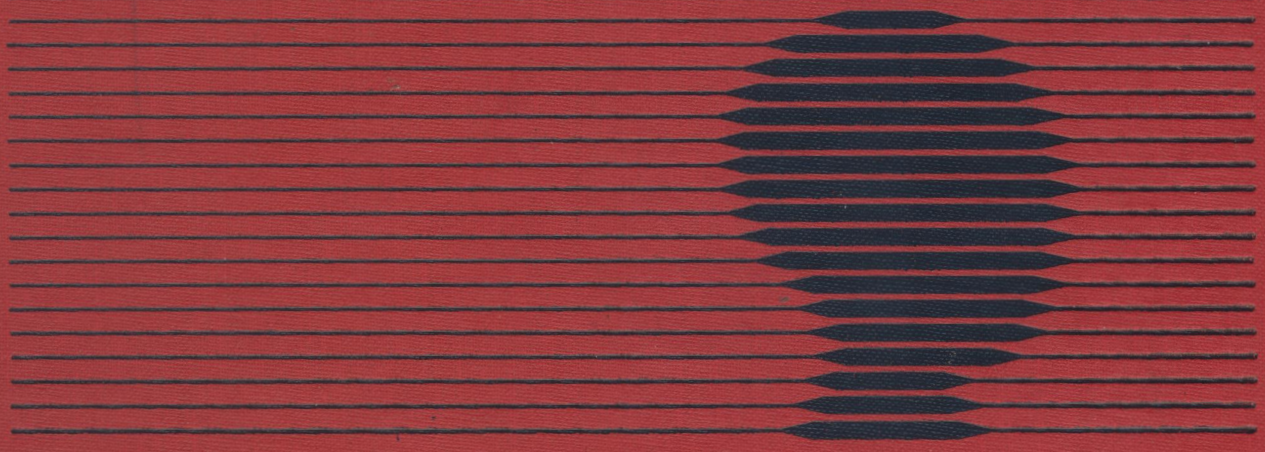
Management of Head and Neck Cancer

A Multidisciplinary Approach

Second Edition



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Nicholas J. Cassisi

J. B. LIPPINCOTT COMPANY

Second Edition

MANAGEMENT OF HEAD AND NECK CANCER

A Multidisciplinary Approach

Edited By

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The authors and publisher have exerted every effort to ensure that drug selection and dosage set forth in this text are in accord with current recommendations and practice at the time of publication. However, in view of ongoing research, changes in government regulations, and the constant flow of information relating to drug therapy and drug reactions, the reader is urged to check the package insert for each drug for any change in indications and dosage and for added warnings and precautions. This is particularly important when the recommended agent is a new or infrequently employed drug.

MANAGEMENT OF HEAD AND NECK CANCER

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This text is dedicated to our mentors,
Gilbert H. Fletcher, M.D., and
Joseph H. Ogura, M.D.,
who have contributed so much to the
understanding and management of
head and neck cancer, as well as
giving us an excellent start.

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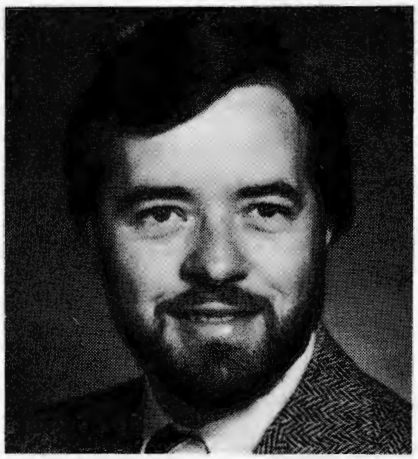

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PREFACE

Management of Head and Neck Cancer: A Multidisciplinary Approach is a result of 18 years of close cooperation between the editors in the management of head and neck neoplasms at the University of Florida. Lip service is often given to cooperative multidisciplinary cancer management, but for us it is a reality. With the exception of Ian Tannock and Andrew Harwood, the authors are faculty or trainees of the University of Florida.

This second edition represents our current philosophy in the management of head and neck tumors. We recognize that there are many successful treatment alternatives in the management of head and neck cancer and do not argue that our approach is the only one or the best. Treatment results are reviewed yearly to determine areas that need change or refinement. To base treatment recommendations on the last "success" or "failure" is irrational. We have outlined our usual treatment recommendations in the various chapters, but never hesitate to individualize recommendations based on the specific problem. After all, there are approximately 35 different anatomical sites in the head and neck. Each site may present with a myriad of clinical situations and each patient with different personal requirements. It is clearly impossible to cover every clinical situation in the text, and therefore the physician must remain flexible and innovative to individualize where needed.

Our general approach to the management of the neck is presented in Chapter 6, "Management of the Neck for Squamous Cell Carcinoma." Special situations regarding the neck are considered in the individual chapters.

Space is allocated preferentially to radiation therapy over surgery, because there are numerous texts emphasizing the surgeon's viewpoint and surgical technique. This is not to be construed that we fail to recognize the importance of surgery, but rather to highlight the possible uses and advantages of radiation therapy.

Computed tomography and magnetic resonance imaging have made a dramatic change in the management of head and neck cancer over the past decade. Dr. Tony Mancuso, "ace" head and neck radiologist, has made a major contribution to this edition.

Rodney R. Million, M.D.

Nicholas J. Cassisi, D.D.S., M.D.

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In the first edition it was decided to obtain outside reviews of each chapter to make the book as free of errors as possible. We again thank Robert D. Lindberg, M.D., who was the primary consultant for the first edition. We thank Gilbert H. Fletcher, M.D.; H. Rodney Withers, M.D., Ph.D.; Helmuth Goepfert, M.D.; Oscar M. Guillamondegui, M.D., F.A.C.S.; K. Kendall Pierson, M.D.; Dempsey S. Springfield, M.D.; William F. Enneking, M.D.; William F. Hanafee, M.D.; Glenn E. Sheline, Ph.D., M.D.; and Thomas Ervin, M.D., for their helpful review of portions of the first edition. Lynn Million Smith, M.D., reviewed the pediatric chapter for the second edition.

A. W. Peter van Nostrand, M.D., F.R.C.P.(C), once again permitted us to use his excellent whole-organ sections of the larynx, pyriform sinus, nasopharynx, and paranasal sinuses.

Professor Ugo Fisch allowed us to reproduce the cervical lymphangiograms from his book, *Lymphography of the Cervical Lymphatics*.

William R. Panje, M.D., F.A.C.S., supplied the original photographs of five midface skin cancers.

Our editorial staff is headed by Patricia J. McCarty. Hank Higgins, research clerk; Dorothy Davis, word processor operator; and editorial assistants Nancy Tortora, Catherine Elverston, Katie McCarthy, and Anne Taylor-Covell all worked on the second edition. Without their dedicated help, this book would have been impossible.

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MANAGEMENT OF HEAD AND NECK CANCER

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1

HISTORY OF DIAGNOSIS AND TREATMENT OF CANCER IN THE HEAD AND NECK

PATRICIA J. McCARTY AND RODNEY R. MILLION

HEAD AND NECK CANCER IN EARLY PEOPLES

Treatment of Head and Neck Cancer by Primitive Peoples

The history of the earliest treatment of cancer is obscure. To make conclusions about early primitive populations based on observations of later primitive populations is risky. The findings described below can only suggest possibilities about ancient practices.

In a review of surgery practiced by primitive peoples, Ackerknecht[6] theorized that their failure to develop surgical therapy was due mostly to the widespread magical beliefs about the causation of disease. Primitive peoples would use sophisticated techniques for ritual mutilation or punishment without applying these same techniques in situations in which they might have saved lives.

Ackerknecht[6] called the Masai of East Africa the "primitive master surgeons." They and some of their East African neighbors performed many kinds of operations with iron knives, using thorns for sutures and tendons to suture vessels to stop bleeding. Surgeons formed a separate occupational class and operated on people and animals. Some of the head and neck procedures carried out in primitive Africa included scarification of inflamed tonsils, enucleation of eyes, excision of neck glands in cases of trypanosomiasis, cauterization of neck tumors, and removal of the uvula. The natives of one Polynesian island were reported to operate successfully on lipomas, tuberculous neck glands, and old ulcers; using only shark teeth as scalpels.[6]

In America, the pottery of the ancient Peruvians shows numerous instances of mutilated noses and lips, but these may have resulted from disease processes rather than surgical operations. If the mutilations were deliberately inflicted, the purpose was more likely punitive or religious rather than medical, although surgical treatment of nose or lip cancer could have produced this appearance.[6]

Paleopathologic Evidence for Head and Neck Cancers

The Kanam mandible, a fossilized mandibular fragment found in East Africa by Leakey, was deformed by an irregular lesion that was "fairly extensive, extending onto the lingual and labial surfaces of the jaw in the region of the symphysis."[19,94] This fossil probably dates back to the Middle Pleistocene (more than 500,000 years ago), making this the oldest known instance of a tumor in a human species. It was interpreted as an osteogenic sarcoma by Lawrence,[93] but others interpreted it as a reaction to trauma.[140]

Benign neoplasms, both primary osteoma and bony reactions to meningioma, hemangioma, fibroma, or nasal polyps, have been described in ancient skulls. One benign neoplasm destroyed most of the nasal bones, the left inner orbit, the left maxilla, and much of the palate in a young adult male in neolithic Denmark; it may have been a juvenile angiofibroma.[19] Some disseminated lesions—either widespread metastases or multiple myelomas—have also been reported.[19,175]

Few ancient skulls have been reported to show evidence of primary head and neck carcinoma. Table 1-1 includes nine such cases, two of which may show evidence of therapeutic efforts. In case 6, from upper Egypt in the Early Christian era, a tumor (possibly nasopharyngeal) had eroded through the pterygoid fossa into the maxillary sinus. A piece of linen cloth was found in the right external auditory meatus, indicating, possibly, that therapy had been performed for severe pain or dis-

TABLE 1-1. Paleopathologic Evidence for Primary Carcinoma and Ameloblastoma in the Head and Neck in Ancient and Medieval Peoples

Geographic Location	Era	Age and Sex	Probable Primary Site	Description of Bone Destruction
1. Tepe Hissar, Iran	3500–3000 BC	Adult man	?	Extensive destruction of the left facial bones (maxilla, palatine, and zygoma) and the floor of the left orbit; obliteration of the left maxillary sinus; penetration of the floor of the left nasal fossa, extending to the right of the midline; all of the left upper teeth and right central incisor missing
2. Egypt	Old Kingdom, III–V Dynasty, 2686–2345 BC	30 to 35-y-old man	Maxillary sinus and palate	Destruction of the left maxilloalveolar regions, part of the palate, the medial and lateral pterygoid plates, and part of the inferior concha; 26 secondary lesions scattered over the skull
3. Northwest of Naga-ed-Dêr, Upper Egypt	VI–XII Dynasty, 2345–1786 BC	35 to 45-y-old woman	Nasopharynx most likely; possibly nasal cavity, oral cavity, or pharynx	Greater part of the facial skeleton and the sphenoid region of the skull base destroyed; center of the tumor (if growth was symmetric) in the epipharynx to the right of midline; also a small separate honeycomb area on the squamous part of the right temporal bone
4. Southern part of Egyptian Nubia	New Kingdom, 1567–1085 BC	Elderly woman	?	Erosion of the base of the skull affected the left half of the sphenoid bone; also, there were other lesions on top of the vault, including a frontal perforation
5. Nubia	AD 300–600	Man	Nasopharynx or sphenoid sinus	Massive destruction from the cribriform plate back nearly to the foramen magnum, and destruction of almost all of the sphenoid bone, the nasal turbinates and vomer, and the posterior part of the palate
6. El-Barsha, Menya province, Upper Egypt	AD 500 ± 100	30 to 35-y-old man	Nasopharynx or maxillary sinus	Erosion from the pterygoid fossa into the maxillary sinus (piece of linen cloth in ear)
7. Baselland, Switzerland	"Frühmittelalter" period (early Middle Ages)		Ethmoid sinus or skin	Destruction of part of the frontal region—the right upper orbital margin and the nasal bones to the left of the upper orbital margin
8. Caen, France	AD 1100–1200	Man < 40 y old	Maxillary antrum	60 × 40-mm tumor of the right maxilla, extending up to the orbit and down to the nasal orifice; a rectangular hole in the zygomatic bone; all maxillary teeth missing
9. Czersk, Poland	AD 1000–1300	40- to 50-y-old man	Mandible	Expansion lesion of the middle segment of the right side of the mandible; ameloblastoma by gross appearance and x-ray

Notes

Case 1: Skull no. 33-23-36 from Hissar II. Reported (with photograph) by Krogman, who thought destruction was due to "inflammatory condition," perhaps secondary to "sinus infection brought abaut by dental disease."[91] Wells called it "a naso-pharyngeal lesion."[176] Brothwell said destruction "could well be the result of carcinoma."[19] According ta Ho, "There was no description of destruction of bone in the immediate vicinity of the nasopharynx. There are, therefore, no grounds to interpret from these findings that the primary condition could be nasopharyngeal carcinoma."[76]

Case 2: Skull no. 236, Duckworth Laboratory, Cambridge, England. Reported by Wells, who examined the skull by x-ray and transillumination.[174] Also pictured by Brothwell, Ho, and Wells.[19,76,177] Ho examined the skull and thought that the primary site was probably the maxillary alveolus or the floor of the maxillary sinus, rather than the nasopharynx, and that the most likely diagnosis, especially in view of the secondary lesions in the cranial vault, should be multiple myeloma.

Case 3: Skull no. 12-5046, tomb 217, cemetary 100, Lowie Museum of Anthropology, Berkeley, CA. Reported with photographs by Strouhal.[158]

Case 4: From grave no. 204/15. El Batrawi called the lesion an "unexplained erosion of the base of the skull."[50] Judging by pictures in el Bratrawi's report, Brothwell thought it should be reexamined as a possible neoplasm.[19]

Case 5: X-group skeleton no. 188B. Derry described in detail.[46] Elliot Smith and Dawson said the lesion was suggestive of "epithelioma of the naso-pharynx."[51] The lesion was pictured by Brothwell.[19] Ho said that the "site and appearance of the destruction are consistent with a diagnosis of either carcinoma of the sphenoid sinus or nasopharyngeal carcinoma."[76]

Case 6: Skull no. 58. Reported by El-Rakhawy and coworkers and described by Strouhal.[53,158]

Case 7: Skull D, 10, Kantonmuseum, Liestal. Described as postmortem erosion by Hug.[80] Brothwell studied the skull and believed the destruction was caused by a destructive tumor in the region of the frontal sinuses.[19]

Case 8: Ossuary under Chapelle Saint-Georges inside Chateau de Caen. Reported with photographs by Dastugue.[42]

Case 9: From a medieval burial ground; only the mandible was preserved. Reported with photographs by Gladykowska-Rzeczycka.[67]

charge.[53] In case 8, a skull found in the ossuary of a 12th-century French castle revealed that a huge maxillary tumor had invaded the orbit and nose. A rectangular hole had been cut in the man's zygomatic bone an appreciable time before his death, judging by the healing that had taken place in the bone, which may represent an effort to relieve excruciating pain.[42]

The evidence for tumors in ancient skulls is frequently debatable, because trauma, infection, and postmortem damage can result in similar bony changes. There is also argument about the incidence of head and neck cancer in the ancient past. Because few people lived beyond 50 years of age, there was not a large population in the most cancer-prone age group. There may actually have been a relatively high incidence of nasal, nasopharyngeal, or paranasal sinus cancers in some ancient populations. Wells, for instance, discussed the possible relationship of inhalation of wood smoke or peat smoke to the occurrence of sinusitis and sinus cancer in people who lived in poorly ventilated huts.[177] He found a 6.8% incidence of changes resulting from severe sinusitis in a series of Anglo-Saxon skulls.

Head and Neck Cancer in Ancient Civilizations

The oldest medical documents, on Egyptian papyri, describe tumor treatment. The Edwin Smith papyrus, a surgical treatise written about 1600 BC or earlier, mentions what is probably breast cancer, but no head and neck tumors. The Ebers papyrus, written about 1500 BC or earlier, describes medical rather than surgical treatment; it is essentially a collection of drug recipes with a fragmentary description of the diseases they are intended to treat.[26] Among the diseases mentioned are an "eating ulcer of the gums" and an "illness of the tongue," descriptions too vague to allow us to decide whether the lesions were neoplastic.[31]

The ancient Greek physicians definitely recognized cancer, especially breast cancer. Around 400 BC, Hippocrates referred to what was probably tongue cancer in his *Prorheticon* when he described chronic ulcers of the edge of the tongue, which he said were common and related to the presence of sharp teeth rubbing against the tongue.[114] Hippocrates also reported that "a man who had a carcinoma in his pharynx and was cauterized by us got well."[108]

The Greco-Roman physician Asklepiades is credited with the use of tracheotomy, probably for diphtheria, around 50 BC.[112] He rejected the Hippocratic doctrine of the four humors and was the founder of the Methodist school of medicine in Rome.

About AD 30, Celsus compiled an encyclopedia of the Roman medical knowledge of his time. He described cancer treatment in this way: "Some physicians used caustic remedies. Some cauterized, and others operated with the knife. The remedies, however, never did any good to anybody."[149] Nevertheless, he described an operation for cancer of the lip and, probably, plastic repair of the lip after removal of the tumor.[73] He also wrote about necrotic ulcers that caused foul breath, which were treated with cauterization. He advised splitting the nostril if necessary to treat ulcers in the nose and suturing the nostril. Such ulcers, he said, would heal slowly.[119] These ulcers must have had a variety of causes; if they were malignant, it is unlikely that they would have healed. Celsus also mentioned many other head and neck procedures, such as uvulotomy, nasal polypectomy, and an operation for removal of goiter. He wrote that hardened tonsils might be scratched out with a fingernail or hooked up and dissected out.[119] He also described the wiring of loose teeth and the use of a dental mirror.[150]

Local drug therapy during Celsus' time included the use of metallic salts (copper and lead), sulfur, and arsenic pastes. Such remedies were commonly used on ulcers of any type and were therefore applied to malignant ulcers as well.[149] The arsenic paste, which was used into the 20th century, might actually have had some true antineoplastic effect.

By the time of Galen (AD 129 to 199), the humoralists were ascendant, and Galen's great synthesis and forceful development of the humoral theory made it the basis for medical practice for some 1500 years. In this theory, cancer was supposed to be the result of overproduction of "black bile" and its local thickening or concentration, which was particularly likely to occur on the face, lips, or breast.[106] Because the local lesion was thought to be a manifestation of systemic disease, local treatment such as surgery was discouraged. Unsuccessful surgical treatment would have supported the theory.

Galen, an accomplished surgeon, gave the following instructions for cancer operations: "If you attempt to cure cancer by surgery, begin by cleaning out the melancholic tumor by cathartics" (ie, first treat the systemic disease). "Make accurate incisions surrounding the whole tumor so as not to leave a single root. Let the blood flow and do not check it at once, but make pressure on the surrounding veins, so as to squeeze out the thick blood. Then treat as other wounds."[108] He advocated the use of cautery, both to achieve hemostasis and to destroy any remnants of cancer.[128] He also described the surgical removal of a goiter and of nasal polyps, and uvulectomy was apparently a common operation, performed for a variety of conditions.[172] In passing, Galen mentioned a hard tumor of the tongue, which he said he would discuss in a later book; unfortunately, the later book has been lost.[114]

Galen was also an experimental physiologist and anatomist. He demonstrated the function of the recurrent laryngeal nerve, proving the connection of the vocal cords to the brain. He cut the nerve in a pig (in an attempt to determine whether the nerve had any effect on respiration) and was surprised to find that, although it continued breathing, the pig could no longer squeal. He repeated the experiment in dogs, goats, and monkeys with similar results, and he described accidental severance of the nerve in patients during goiter operations, which rendered them mute also.[172]

Galen also described accurately the anatomy of the throat: the thyroid, cricoid, and arytenoid cartilages and the epiglottis; their ligaments; the muscles of the larynx and nearby structures; and the tensing and stretching of the vocal cords.[172]

The only other ancient medical writings having any pertinence to the modern Western treatment of cancer are the works of the ancient Indian physicians, especially the legendary Sushruta. In his work, he combined the system of hygiene, preventive medicine, and a healthful regimen of living taught by the high-caste Brahmin physicians with the practical techniques of the surgeons, who had previously been illiterate and of low caste.

Sushruta described the removal of tumors. He sutured wounds with flax, sinews, or hair, using a variety of

needles. In his writings, he listed 101 blunt and 20 sharp surgical instruments. Cauterization and methods of hemostasis were described, and anesthesia was produced by alcoholic drinks.[170]

The early Indian surgeons developed great skill in plastic surgery, partly because the ears and nose were frequently amputated as a punishment, even for minor infractions, and partly because defects often occurred as a result of the constant warfare. Sushruta described in detail his method of reconstructing a missing nose:

> First the leaf of a creeper, long and broad enough to cover fully the whole of the severed or clipped off part, should be gathered; and a patch of living flesh, equal in dimension to the preceding leaf, should be sliced off (from down upward) from the region of the cheek and, after scarifying it with a knife, swiftly adhered to the severed nose. Then the cool-headed physician should steadily tie it up with a bandage decent to look at and perfectly suited to the end for which it has been employed. The physician should make sure that the adhesion of the severed parts has been fully effected and then insert two small pipes into the nostrils to facilitate respiration, and to prevent the adhesioned flesh from hanging down.[159]

The wound was treated with powders, bandaged in cotton, and sprinkled with sesame oil. The patient was given clarified butter to drink, was anointed with oil, and was treated with purgatives after his meals were digested. When the donor site was healed, the nose could also be considered healed. If adhesion was incomplete, the area could again be scarified and bandaged together. Also, the surgeon could attempt to elongate or shorten the new nose if its length was not quite right. Sushruta also described reconstruction of severed lips and earlobes.[181]

MEDIEVAL AND RENAISSANCE CANCER TREATMENT

The early medical writings, although fragmentary and often obscure in meaning, were the basis of Western medicine until sometime after 1600. As the Roman empire disintegrated, Byzantine and later Arab physicians inherited the Egyptian, Greek, and Roman medical treatises and preserved them, with occasional personal additions, through the centuries. These medieval writers mentioned cancer of the head and neck area, usually of the tongue or lips, even less often.

Probably the greatest Byzantine medical writer was Paul of Aegina (seventh century). His work is primarily a compilation of earlier writings, but he was himself a practicing surgeon, and he occasionally inserted information from his own experience. His works were translated into Arabic, and, with other similar Byzantine works, they formed the basis of Arabic medicine. He advocated bleeding, cauterization, and open treatment of surgical wounds. In his discussion of tracheotomy, he first quoted Antyllus, a great Roman surgeon (circa AD 150) whose works are otherwise lost:

> Wherefore, bending the patient's head backwards, so as to bring the windpipe better into view, we are to make a transverse incision between two of the rings, so as that it may not be the cartilage which is divided, but the membrane connecting the cartilages. If one be more timid in operating, one may first stretch the skin with a hook and divide it, and then, removing the vessels aside, if they come in the way, make the incision.

Paul continued with a personal observation:

> We judge that the windpipe has been opened from the air rushing through it with a whizzing noise, and from the voice being lost. After the urgency of the suffocation has passed over, we pare the lips of the incision so as to make them raw surfaces again, and then have recourse to sutures, but sew the skin only, without the cartilage.

Paul[130] also discussed neck dissection for scrofulous (but not for carcinomatous) neck nodes.

The 10th-century Spanish Muslim physician Albucasis (Abu'l-Quasim), of Córdoba, wrote the only medieval Arabic textbook of surgery. Most of his book was taken from Paul of Aegina, but he inserted some case histories from his own practice. He depended heavily on Galen. Albucasis said that cancer "should not be attacked with a sharp instrument, at least not when it is so fixed in an organ that it cannot be radically excised," and he advocated cauterization for cancer excision and hemostasis.[20,181]

Avenzoer (Ibn Zuhr), of 11th-century Córdoba, was the only Muslim physician actually to advance the knowledge of cancer through his descriptions of cancer of the stomach and esophagus. He diagnosed and treated cancer of the esophagus with sounds or dilators made of silver or tin.[73]

This garbled collection of translations of ancient texts and later additions was translated again—this time from Arabic into Latin. Other medical texts were preserved by the Byzantines. Both Arabic and Byzantine medical texts were available to physicians at Salerno (in southern Italy), which by the late 11th century had become a center of medical knowledge, particularly of practical surgical knowledge.[113] In his *Surgery*, compiled in 1170, Master Roger of Salerno taught that cancer should be completely excised by knife or cautery, if possible, or that it should be otherwise treated with caustic ointments. If located close to major nerves or arteries, it was best left alone. Scrofulous neck nodes were excised if they were enlarged, but apparently cancerous nodes were not.* Goiter was treated first with a drug that contained ashes of sponge and seaweed (both containing iodine), but if this treatment failed, the goiter was removed surgically.[37] Roger gave an illustration of the special forceps he used for uvulotomy, which apparently was still a common operation, and, in an early effort at producing surgical anesthesia, the Salernitan surgeons described the use of the "soporific sponge," which was soaked in the juice of hyoscyamus and poppy.[37,136]

In the 1500s, the work of the first modern anatomists began, with Italy as the center of activity. It was at this

* Hayes Martin[114] noted that "Up until the latter part of the 19th century, most cervical lymphadenopathies were grouped under the general term 'scrofula,' especially if they were associated with 'eruptions' of the skin or oral mucous membranes. Under such conditions, it is obvious that errors in diagnosis would be likely to occur in the cases of oral cancer in which cervical lymphadenopathy appeared as the first or as one of the early symptoms."

time, for example, that the anatomy of the ear—the eustachian tube, tympanic membrane, and semicircular canals—was elucidated. The cerebral vessels and cranial nerves were described, as were the larynx and the musculature of the pharynx and palate. The great anatomists were practicing surgeons as well. Fallopius (Gabriele Fallopio), for instance, devised a polyp snare, "a steel wire looped inside a tube through which it could be drawn, thus cutting off the polyp."[119] Perhaps the most renowned Italian surgeon-anatomist was Fabricius of Acquapendente (Gerolamo Fabrizio). Among his surgical achievements were the attempt to improve the technique for tracheotomy, the development of a silver cannula for feeding through the nose, and the invention of an angulated scissors for the extraction of polyps. His surgical works, one section of which was entitled "Tumors," were reprinted every few years until 1729.[22,102]

Plastic surgery was badly needed during the 1500s to replace missing or mutilated lips, ears, palates, and, particularly, noses. There was a virulent epidemic of syphilis, warfare resulted in blade and arrow wounds, and punitive mutilation was widely practiced. Pope Sextus V (1521 to 1590), for example, ordered the amputation of the nose as a punishment for theft. The most famous 16th-century plastic surgeon was Gaspare Tagliacozzi of Bologna, although he probably derived his techniques from other Italian surgeons, such as the contemporary Vianeo family of Calabria, Aranzio of Bologna, the Sicilian Brancas (father and son) from the previous century, and others. The elder Branca used flaps of skin from a patient's face to form a nose (the Indian method). His son used the skin of the patient's arm and extended the method to repair lips and ears as well. Most of these early practitioners guarded their methods as family secrets, but Tagliacozzi of Bologna, whatever the origin of his techniques, publicized his work and found his services in great demand. He published a book detailing his methods in 1597, complete with illustrations (Fig. 1-1).

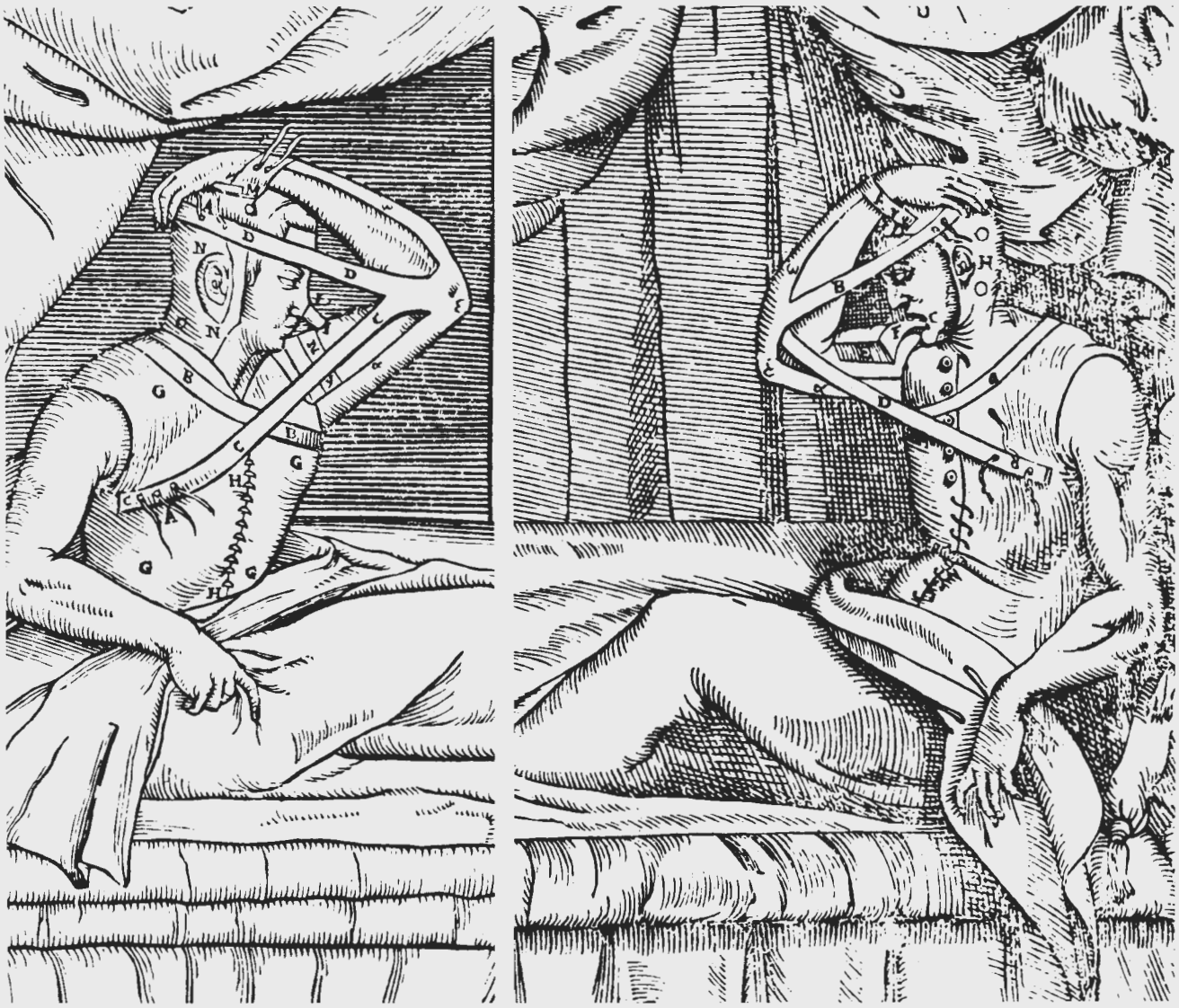

Figure 1-1. Tagliacozzi's method of restorative surgery for the nose and lip, illustrated in his *De Curtorum Chirurgia per Insitionem* (1597). (*Left*) Rhinoplasty. (*Right*) Lower lip restoration. (*Left* from Margotta R. The story of medicine. New York, Golden Press, 1968:180; *right* from Singer C, Underwood EA. A short history of medicine, ed 2. New York, Oxford University Press, 1962:99)

For restoration of the nose or lip, he cut a flap from the anterior surface of the arm and applied it to the appropriate area. The arm was held in place by a sort of sling until the flap adhered to the face. To replace a missing ear, he used sliding flaps, taking a section from the parietooccipital region to form the upper part of the ear and a section from the upper triangle of the neck to form the lobe.[21] Tagliacozzi's success was not approved of by the religious authorities of the day, who thought it derived from the Devil. After his death, nuns were said to have heard a voice at night saying that Tagliacozzi was damned, and his remains were removed from consecrated ground. Restorative surgery was not practiced again for some 200 years.[21,102,113,150]

Another approach used at this time was to construct a prosthesis to replace missing parts. The Danish astronomer Tycho Brahe lost most of the bridge of his nose in a duel in 1566 and replaced it with a prosthesis made of a copper–silver alloy, painted to match his skin and glued in place. He was a nobleman, wealthy and vain of appearance, and he would undoubtedly have sought surgical repair of the defect had such been available.[8,97]

In the mid-16th century, Amatus Lusitanus published an account of his method of replacing a part of the palate that had been destroyed by syphilis:

> I ordered a goldsmith to prepare a golden-headed nail; the head of the nail was round and broad enough to close the total circumference of the foramen, whereas the tip of the nail was narrow and round; in its center an ear, lentil-shaped, was prominent. To the said tip, or spike, of the nail a small sponge was fitted, and this the patient had to introduce at the same time into the foramen where it expanded with moisture and so remained fixed in position. Thereby he was able to speak correctly as if nothing ailed him.[98]

Ambroise Paré, a 16th-century French surgeon, was ingenious in devising prostheses for the soldiers who were mutilated by war, which by his time included the use of gunpowder. He published illustrations of artificial eyes, noses, and ears that he had devised (Fig. 1-2), and he even made an artificial tongue, which was attached by a string to the patient's neck.[127,138] He apparently applied these methods to cancer patients also. He wrote of the "erosion or eating of a pestulent carbuncle or ulcerated cancer so that the teeth may be seen to lie bare with great deformity," and he said that "If the loss or consumption of lip be not very great it may be repaired by that way I have described in the cure of hare lips or ulcerated cancer, but if it be great, then there must be a tip of gold made for it."[138]

One of Paré's case reports describes his operation for lip cancer in a 50-year-old man:

> Pass a threaded needle through the cancer so the thread held in the left hand can lift and control the cancer without any of it escaping. One can then cut to good flesh with scissors in the right hand; and cut so that a layer of good flesh of the lip remains to serve as a base and foundation for regeneration of flesh in place of the portion amputated, supposing the cancer has not taken root and spread from top to bottom. This done, having let enough blood flow from within and without, at the right and left of the amputation, make deep enough incisions with the razor so that later, when one would draw together and unite the edges of the wound, as in the case of harelip, the flesh would be more obedient to the thread and needle.[74]

The greatest of the German surgeons of the time was Fabricius Hildanus (Wilhelm Fabry of Hilden, near Düsseldorf, who practiced in Germany and in Berne). In his *Century of Surgical Cases,* he described a number of cases

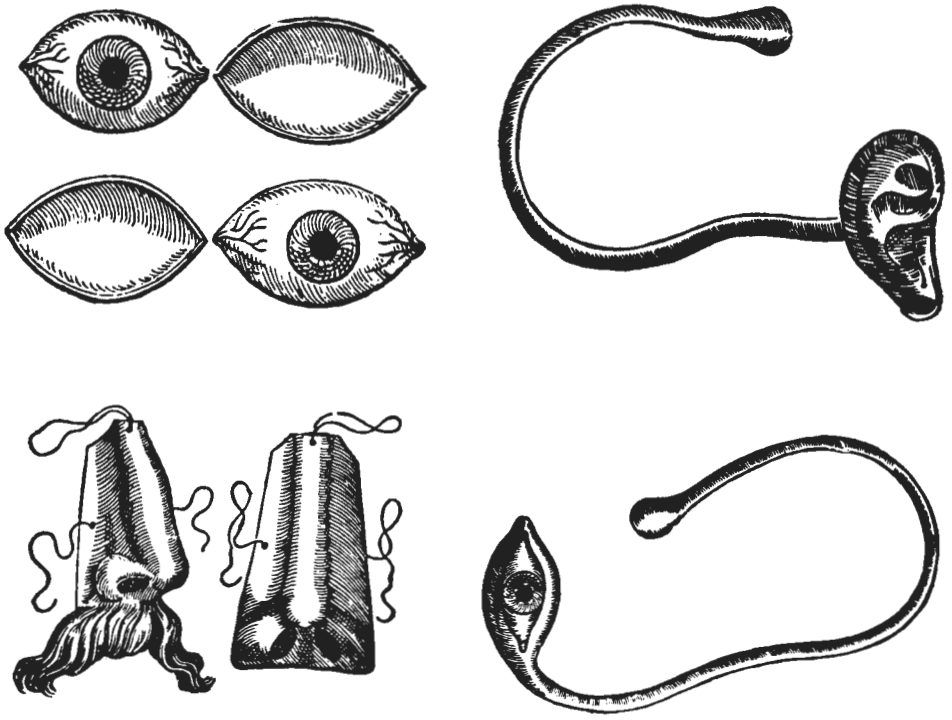

Figure 1-2. Examples of prostheses devised by Paré, from *Of the Means and Manner to Repair or Supply the Natural or Accidental Defects or Wants in Man's Bodie.* (Roberts AC. Facial reconstruction by prosthetic means. Br J Oral Surg 1966;4:157–182)

of cancer in which he carried out extensive operations.[73] His cases of head and neck cancer (or tumor) included the removal in 1605 of a "fleshy excrescence" from the external ear canal of a 19-year-old girl who had a 10-year history of otorrhea and deafness but no pain. He placed ligatures, which he tightened daily with special forceps of his own design, around the pedicle of the tumor. On the seventh day of treatment, the tumor came away, and the root was cauterized twice daily for 2 days. Eight years later, the patient was still well.[86]

Like Paré, Fabricius invented surgical instruments and devised prostheses. For example, he invented an instrument for blowing styptic powder onto an enlarged uvula: a tube, bent at one end, with a small copper spoon attached at that end for holding the powder and a leather bag attached at the other end for an insufflator. He invented a complicated instrument for removal of nasal polyps, and he improved a tube used to remove foreign bodies from the pharynx. He also described a successful palatal obturator.[86]

Paré and Fabricius Hildanus were practical men rather than scholars, barber-surgeons rather than university physicians. They both realized the importance of the study of anatomy, the area of great medical breakthroughs in their time. Galen's humoral theory still held sway in more scholarly circles and offered little basis for any kind of realistic cancer treatment.

THE DEVELOPMENT OF PRESENT-DAY CANCER OPERATIONS

In the late 18th century, Paris became the center of the medical world. The Parisian physicians discarded much of the humoralist system in favor of "localism," the idea that disease, including cancer, might have a local rather than systemic origin and could therefore be treated in its early stages. This provided a theoretical basis for the development of cancer surgery. The Parisian physicians were strong believers in postmortem dissections and developed the study of gross pathology. In keeping with the 18th-century penchant for classifying, they began to sort out cancer from other kinds of growths and ulcers and even to recognize different kinds of cancer. Parisian medicine was almost totally clinical in its orientation, however, and resisted the new areas of microscopy, experimental physiology, and medicinal chemistry. The Germans were not so conservative, though, and they were able in their universities to combine the best of the Parisian emphasis on physical examination, statistics, and macroscopic pathologic anatomy with the new equipment (such as the achromatic microscope) and experimental methods. Thus, Germany became the new center of the medical world, particularly for surgery, in the 19th century.[5]

In the mid-19th century, anesthesia and antisepsis were developed, both of which were crucial for the development of modern surgery. First was anesthesia, the use of which began in the 1850s. It made patients more willing to undergo operations and enabled them to lie quietly while the surgeon did careful, methodical work. The great advances in operative technique began with this innovation, and the beginnings of all the modern, complex operations for head and neck cancer can be traced to this era.[119] Beginning in the 1870s, antibacterial methods began to be adopted—first, antisepsis for a brief time; then, asepsis. As a result, a patient who survived an operation was less likely to die of infection.

Along with the development of anesthesia and antisepsis, a third necessity for effective cancer therapy was the development of microscopic pathology. The 19th-century technical revolution in this field was described by Long:

> In the first decades of the 19th century, men were cutting slices of fresh tissue by hand and examining them under the microscope. At the close of the century, they were hardening tissues in appropriate fluids, embedding them in rigid materials to facilitate cutting, slicing them with machinery into incredibly thin sections, and coloring them with combination stains which sharply contrasted the varying cellular elements.[106]

John Hughes Bennett, a surgeon, lectured on histology at Edinburgh University beginning in 1841 and included microscopic demonstrations of morbid histology. Hughes Bennett published a book about cancer in 1849 that included, for the first time, both clinical case histories and microscopic descriptions of tumors.[73] His description of the relationship of clinical medicine and microscopic pathology has a modern ring: "It is not the recognition, by means of the microscope, of certain cells and fibers, which will enable us to assert with certainty the existence of Cancer; but that their detection in particular places, and accompanying peculiar forms of growth, permits us to do so."[81]

The great systematizer of microscopic pathology was Rudolf Virchow. In his greatest work, *Cellular Pathology* (1858), Virchow asserted that all cells arose from preexisting cells but that sometimes normal cells could transform into malignant ones.[106] He believed that the malignant cells were localized to one area in the beginning. As Ackerknecht[4] has said, "The whole emphasis with Virchow was on local causes, local beginnings of tumors." This concept encouraged the use of surgery at the earliest stage of the disease. Virchow thought that metastases were caused by a chemical produced by tumors rather than by transported tumor cells, and he thought that carcinoma arose from connective rather than epithelial tissue (although he was less sure of this later in his life, after Thiersch, Waldeyer, and others had demonstrated otherwise).[4]

The great surgeons of the late 19th century operated with increasing confidence and ingenuity. In the time of Paré and Fabricius Hildanus, surgery was a distasteful profession on the borderline of reputable medical practice, but, by the late 19th century, surgery had become the main focus of advancing medical science. This was the start of the current age of cancer therapy.

Oral Cancer

In the Middle Ages, the oral tongue was often cut, torn, or burned off as a punishment for heresy or *lese majesty* or to prevent the telling of secrets. According to Hayes Martin,[114] the tongue was drawn from the mouth, usually by a sharp hook, and the protruding portion was cut off from below. Many of the victims survived, especially after it was found that the use of a red-hot knife resulted in less bleeding. Some of the victims had enough tongue musculature remaining to enable them to speak. These reports must have encouraged surgeons in their first ef-

forts to treat tongue cancer and the other serious afflictions of the tongue that were probably even more common in those days, such as gangrene, syphilis, or congenital macroglossia. Some of the patients recovered, but even those who survived the operation itself frequently died later of infection. Several early operations for tumors of the tongue were reported. In 1664, Pietro de Marchetti of Padua, who was also known for the resection of ulcers or cancers of the lip and gingiva, cut and burned away a hard tumor "the size of a hazel nut" from the underside of the tongue. In 1676, the English surgeon, Richard Wiseman, described two cases of fungating oral cancer in his *Chirurgical Treatise.* He cauterized the tumors, but both patients had neck node metastases and died of their disease shortly thereafter.[3,25,116]

In the 18th century, there were scattered reports of operations for tongue tumors by German, English, Italian, and French surgeons. Their techniques varied: some used a knife, some used scissors. Sometimes, the affected portion of the tongue was tied off with ligatures. Some surgeons had an assistant hold the patient's tongue with a piece of linen; others used forceps. They controlled bleeding through cautery or the application of ice or a caustic.[25] The major proponent of glossectomy at this time was the French surgeon, Antoine Louis, who, in 1759, improved operative hemostasis by ligating the vessels that supplied the involved portion of the tongue before the operation.[3]

In the late 1700s, Benjamin Bell described operations for tongue, lip, and buccal cancers in his book, *A System of Surgery.* This Edinburgh surgeon wrote that "cancers, in very few instances, perhaps none, ever arise from a general affection of the system; but, on the contrary, are, at their first appearance, almost always local."[15] He reported that although "cancers occasionally occur in every part of the body," the "underlip is more frequently attacked with cancer than any other part of the body." He blamed most treatment failures on delay in performing an operation. Some of Bell's precepts for treating cancer have held up amazingly well for 200 years. He advised using a scalpel rather than caustics or pastes, saying that the surgeon should "extirpate every part that is diseased," including any part adherent to the tumor, if possible: "Even every indurated gland in the neighborhood of a cancerous sore, should just as certainly be taken away as the ulcer itself; for if allowed to remain, a return of the disease may with certainty be looked for." If it was not possible to extirpate all the disease, he thought the operation should not be performed at all—for instance, when the cancer had spread to other parts of the body, or when it was adherent to the trachea or a large artery. He concluded, "Whatever the risk may be, however, if the diseased parts can be all removed, the operation should certainly be advised. For as we know of no other remedy upon which any dependence can be placed for the cure of cancer it is surely better to submit to some risk than to be left to certain misery and death."[15]

Bell found that lip cancer and cheek cancer could be treated effectively by excision, but that when excision was done in the usual way, "by removing the diseased parts only, and allowing them to heal without drawing them together," the cosmetic and functional result was poor. For cancers extending over the entire lip, no repair was possible after the cancer was removed, but he advocated that, whenever possible, the lip should be repaired by the method he used for harelip (Fig. 1-3). Bell found that by using this method he could remove up to half of the lower lip and still achieve a good functional result and minimal deformity. The same method of repair was advised for buccal cancer, for which his excision began and ended at the angle of the mouth, circling around the lesion. The surgeon was to bring the sides of the cut "neatly together" and pin, which, according to Bell,[15] produced good results.

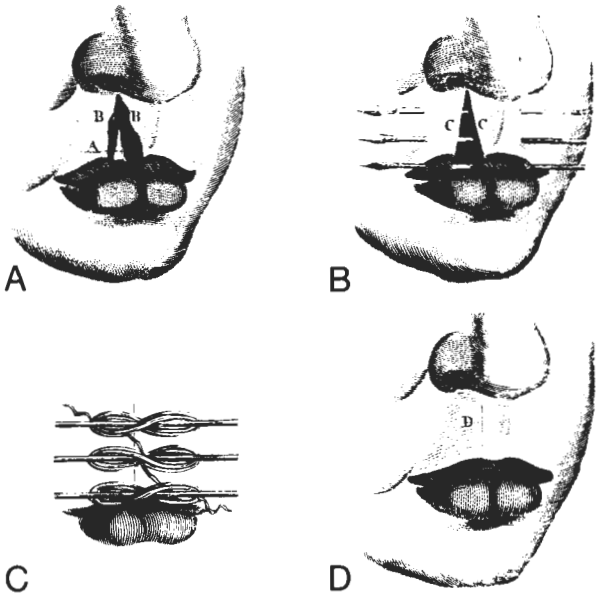

Figure 1-3. Benjamin Bell's method for repair of harelip, which he also recommended for use after excision of lip and cheek cancers. *(A)* Appearance of the defected before repair. *(B)* After cut and insertion of pins. Bell wrote, "Edges of cut ought to be smooth, equal, and exactly of the same length on each side, so that when drawn together, no inequality may be perceptible." The pins were made of gold with removable steel points that were taken off after the ligatures were applied. *(C)* Appearance immediately after the completion of the operation. *(D)* Final result. (Bell B. A system of surgery, ed 6, vol 5, plate XLIV. Edinburgh, Bell & Bradfute, 1796)

Bell allowed that excision of much of the tongue was "a very formidable operation" during which the "symptom of hazard" was the "very sudden discharge of blood." He advised the use of ligatures, which he said could be used more often and at a greater depth in the mouth than was commonly thought. Cautery was a last resort. Bell[15] advised that not every surgeon should attempt operations on the tongue, because they required "that steady, deliberate coolness, which a natural firmness of nerves, conjoined with much experience, alone can give."

Well into the 19th century, the method of strangulating the affected area with ligatures was used in cases of tongue cancer (Fig. 1-4). Patients may have been less afraid of this method than of being cut by a knife, but the method was painful and the danger of hemorrhage and infection was great while the tied-off portion was sloughing. Another treatment method involved the use of caustics. As Butlin and Spencer[25] described in 1900, "The tongue was drawn out, stabs made round the growth, and into the punctures arrowhead-like pieces of chloride of zinc were inserted."

In 1819, Conrad J. M. Langenbeck applied wedge resection, an operation already in use for cancers of the

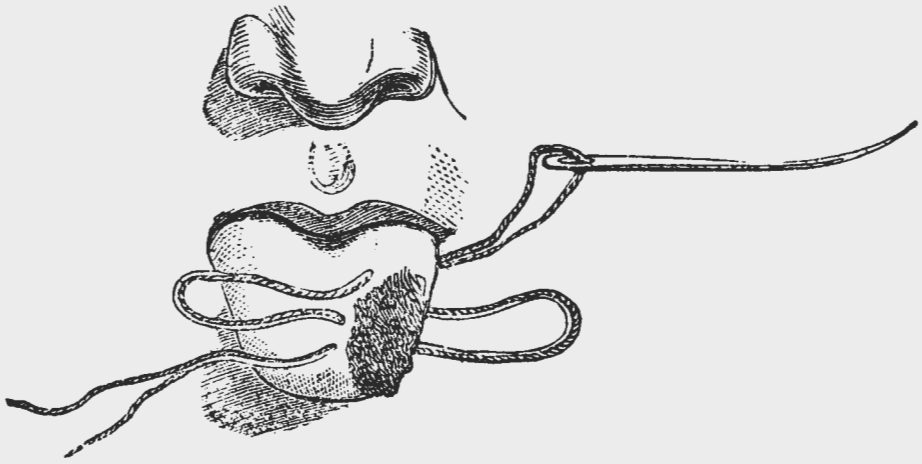

Figure 1-4. Treatment of tongue cancer by ligature. Erichsen[54] described such treatment as follows: "In removing the cancer of the tongue by ligature, the patient should be conveniently seated opposite a strong light. The surgeon then passes a strong silk thread doubled, through the tip of the tongue, by which an assistant draws the organ out of the mouth; a wooden wedge is next placed between the teeth of the upper and lower jaws on the side opposite to that on which the operation is to be performed, and the ligature is then passed by means of an ordinary nevus needle. . . . Care should always be taken to pass them through the healthy tissue of the organ wide of the disease, and they should then be tied very tightly, so as to strangle the mass effectually. Great swelling of the tongue, followed by profuse salivation and some fetor of the breath attend this operation, but the mass, if properly constricted, will slough away in a few days, leaving a large gap that readily fills by granulation." (Erichsen JE. The science and art of surgery, being a treatise on surgical injuries, diseases, and operations. Brinton JH, ed. Philadelphia, Blanchard & Lea, 1854:655)

lower lip, to the tongue. He used sutures to achieve hemostasis. This is considered to have been the first modern, systematic, scalpel excision of tongue cancer.[25,114]

In 1831, Michael Jaeger was the first to divide the cheek to remove a tongue cancer. The patient survived the operation, and the wound healed.[25]

In 1838, Giorgio Regnoli of Pisa removed a patient's tongue through a T-shaped submental incision (a "pull-through" operation; Fig. 1-5). The patient was a 14-year-old girl who had some sort of tumor the size of a hen's egg occupying most of her tongue. He drew the tongue entirely down through the incision, encircled the tongue entirely with ligatures proximal to the tumor, and cut off all parts of the tongue beyond the ligatures with scissors, using cautery as needed. The stump was returned to the mouth; the external wound was left partly open for drainage. The wound was completely healed in 6 weeks, and the patient was able to swallow and to speak with the hypertrophied stump.[25,34]

Philibert Roux reported the case of a 35-year-old man who had had a tumor of the tongue for 5 months. It began as an ulcer and was attributed to smoking. By the time of the operation in 1839, it occupied the entire left half of the patient's tongue. Roux commenced the operation by tying the left lingual artery. He freed the tongue from the floor of mouth, the lower jaw, and the anterior tonsillar pillar, and used a bistoury (a long, narrow knife) from underneath to remove the entire left half of the tongue (ie, he performed a hemiglossectomy). There was no hemorrhage. The patient reportedly "spoke immediately afterward without difficulty," and the wound healed well. In 1900, Butlin and Spencer[25] called this the first "major operation for the removal of a carcinoma-

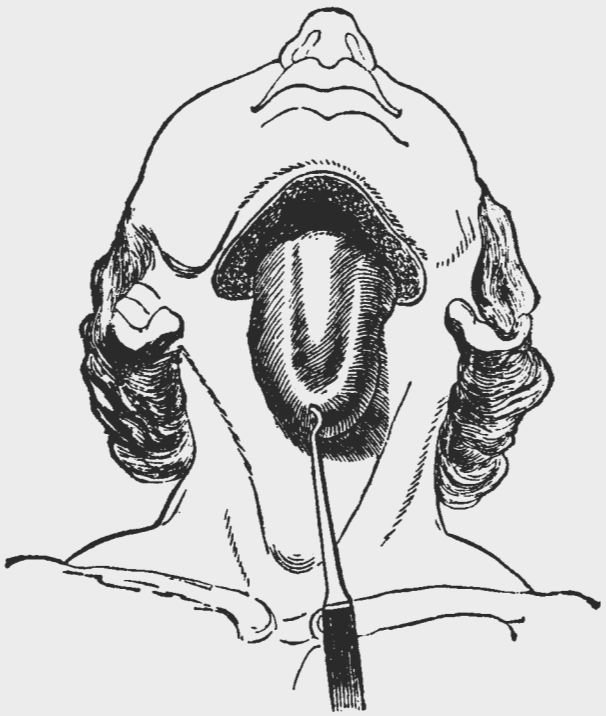

Figure 1-5. The American surgeon, Samuel D. Gross, noted that the "remarkable feat of excising the whole tongue has recently been performed several times in Europe." He illustrated Regnoli's method, calling it the "operation affording the most easy access to the affected organ." (Gross SD. A system of surgery: pathological, diagnostic, therapeutic, and operative, ed 3, vol II. Philadelphia, Blanchard & Lea, 1864:472)

tous tumour such as might be carried out at the present time."

Roux, one of the greatest surgeons of his era, is also said to have divided the lower jaw vertically for an operation on the tongue, the predecessor of later mandible-splitting techniques. Charles Sédillot in 1844 also divided the lower jaw, using an angular cut: "The jaw was fixed [ie, reunited] by a gold plate and by silk threads between the teeth."[25]

During the last half of the 19th century, écraseurs were briefly in vogue for operation on the tongue. An écraseur included a loop of wire or chain that was tightened around the affected part of the patient's body. The procedure was completed more rapidly than a ligature procedure, in hours or even minutes rather than days, and, unlike scalpel excision, produced a sort of tourniquet effect that prevented primary hemorrhage. Severe bruising and frequent infections resulted, however, and the location of the cut was difficult to control precisely; curved needles were sometimes inserted through the tongue to prevent the loop from slipping forward. More than one écraseur could be introduced in various ways, such as through the mouth or from below or after division of the jaw (Fig. 1-6).[25,71]

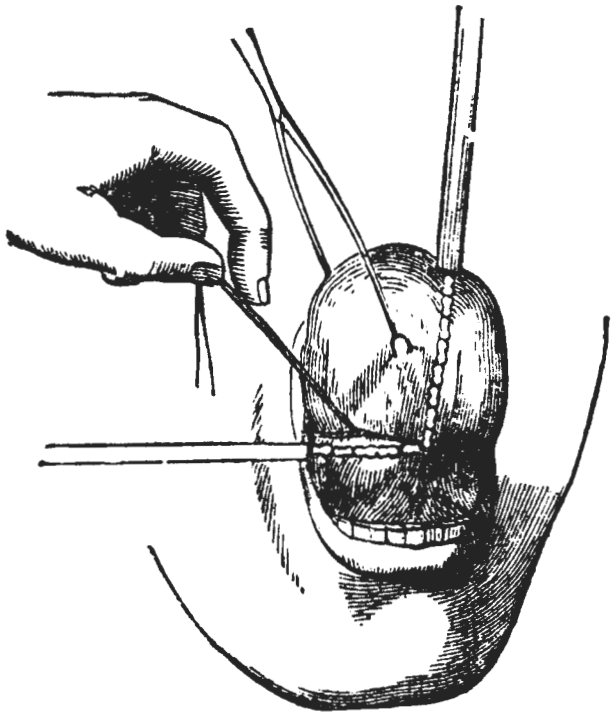

Figure 1-6. Gross illustrated a glossectomy technique using two écraseurs and wrote, "In order to avoid the hemorrhage attendant upon this operation, Chassaignac has proposed the substitution of the écraseur for the knife, and it may readily be perceived that if there are any cases in which such an instrument is applicable, this is one of them. The patient, being under the influence of chloroform, would experience no pain, and the ablation being performed slowly would be almost bloodless." Gross wrote, however, that, in general, little could be achieved by glossectomy, and he did not recommend the operation, writing instead that, "So cruel a procedure could hardly have any other than a fatal termination." (Gross SD. A system of surgery: pathological, diagnostic, therapeutic, and operative, ed 3, vol II. Philadelphia, Blanchard & Lea, 1864:472)

A "galvano-écraseur" was described in the medical literature as early as 1851. It provided a hot, cauterizing cutting surface by means of an electric current that ran through the cutting loop. Although it was at that time a difficult and uncertain instrument, it was used and improved throughout the second half of the century.[25]

All these operations were improved and enlarged upon after the advent of anesthesia. In 1862, Theodor Billroth modified the submental operation by raising a musculocutaneous flap by means of a U-shaped submental incision to gain access to the oral cavity. In the same year, he also divided the ramus of a patient's mandible in two places, turned down the resulting flap of skin and bone to remove the tongue, and restored the bone in place with wire sutures. In 1875, Bernhard von Langenbeck reported the removal of enlarged regional lymph nodes as well as of the tongue cancer, and Billroth also emphasized the importance of removing involved regional nodes. As early as 1881, Billroth's results (reported by his student, Anton Wolfler) indicated that the prognosis in patients with involved nodes that were treated by radical excision was similar to that of patients without clinically involved nodes (ie, the cancer could be cured even after it spread to the regional lymph nodes).[3,25,114]

Theodor Kocher, best remembered for his operations on the thyroid, probably achieved the lowest operative mortality of his day for glossectomy through careful dissection, meticulous hemostasis, and rigorous antisepsis. He used an incision that ran downward along the sternocleidomastoid muscle and up diagonally to form a triangular submental flap. In this way, he had access to the submandibular lymph nodes, the lingual artery, and the oral cavity for removal of any part of the tongue, including the base. His results from 1880 onward brought about the eventual end of the écraseur, ligature, and caustic methods described above.[3] The English surgeon, Walter W. Whitehead, standardized the techniques for operations through the mouth during the late 1800s, achieving a 3% mortality rate in generally less-advanced cases.[25]

By 1900, Butlin and Spencer reported a 12% overall mortality rate in 333 patients who were operated on for tongue cancer in four clinics (two German clinics, Kocher's and Kronlein's; two English clinics, Whitehead's and Butlin's). Mortality for simple removal of some or all of the tongue was 7%; mortality increased to 20% to 25% for operations performed through the submental area and those that involved removing the "glands" beneath the jaw or splitting the jaw. In these same 333 cases, 199 patients were considered to be evaluable for cure; 40 (20%) were free of disease for at least 3 years.[25]

It was during this era that Ulysses S. Grant suffered throat cancer. He is the only American president known to have died of cancer. Grant was a heavy cigar smoker, smoking as many as 12 cigars a day for 20 years or more. He had been a heavy drinker also, although probably not after he achieved positions of responsibility. In June 1885, when he was 63 years old, Grant noticed soreness in his right tonsillar area. His family doctor was in Europe until October, so Grant waited for him to return before seeking treatment. He was immediately referred to a New York throat specialist, John H. Douglas, who kept a diary throughout the months of his devoted attendance on Grant. The diary has not been published, but it is in the Library of Congress. At the time of Douglas' first examination, Grant's tongue was "swollen,

and hard at the base, and to the right side," and the soft palate was inflamed. An enlarged lymph node was noted under the angle of the mandible on the right. In keeping with the custom of that time, Grant was informed that the disease was "serious," but the word "cancer" was not used. Grant was told to stop smoking, which he did. Because his teeth were in bad repair, he was sent to a dentist, Frank Abbott, who pulled three rotten teeth, filled several others, and cleaned the remainder. George F. Shrady, a noted New York surgeon and the editor of the *Medical Record,* was called in for consultation. Apparently, an operation was discussed among his physicians but was never recommended to Grant owing to the extent of the required surgery (removal of the entire tongue and the "glandular structures under the right angle of the lower jaw"), the uncertainty of cure, and the high risk of immediate mortality associated with the operation. Only local treatment was prescribed, including various antiseptic gargles and topical pain relievers. In February 1885, a biopsy was taken (with the use of cocaine as a local anesthetic), and a squamous cell carcinoma was diagnosed.[52] The public clamored for news, and weekly bulletins were issued in the *Medical Record.* As his disease pursued its inexorable course, Grant was writing his memoirs. Victimized by a large-scale swindle, he had been left virtually penniless several months before his illness was discovered. In great distress at the thought of leaving his family destitute, he was persuaded by Samuel Clemens (Mark Twain), a personal friend, to write his memoirs as a means of providing for his family after his death. With cocaine and morphine prescribed for control of pain, Grant worked on the manuscript throughout his illness, despite the constant threat of suffocation and at least one severe hemorrhage. He finally completed his memoirs less than a week before his death on July 23, 1885. The memoirs were published by Clemens and were a great success, eventually providing over $450,000 in royalties for Grant's family.[17,123,155,180]

A more successfully treated case was that of Grover Cleveland, who was president at the time his cancer was discovered. The manner in which his case was handled raises questions about the right of the public to know if the president is seriously ill. In June 1893, the president's physician, Major Robert M. O'Reilly (who was later to become surgeon general), was asked to examine a "rough place" on the president's hard palate. He discovered "an ulcerative surface nearly as large as a quarter with cauliflower granulations."[122,147] O'Reilly called in a surgeon, Joseph D. Bryant, of New York, who found an oval lesion "extending from the inner surface of the molar teeth to within a quarter of an inch of the median line to the roof of the mouth and encroaching somewhat on the anterior part of the soft palate" (Fig. 1-7).[122] A biopsy specimen was submitted to William H. Welch of Johns Hopkins, who apparently diagnosed an epithelial cancer.[122]

The president agreed to have an operation. Because the country was in the midst of the "financial panic of 1893," he insisted on strict secrecy regarding the nature of his illness. He and his associates believed that any

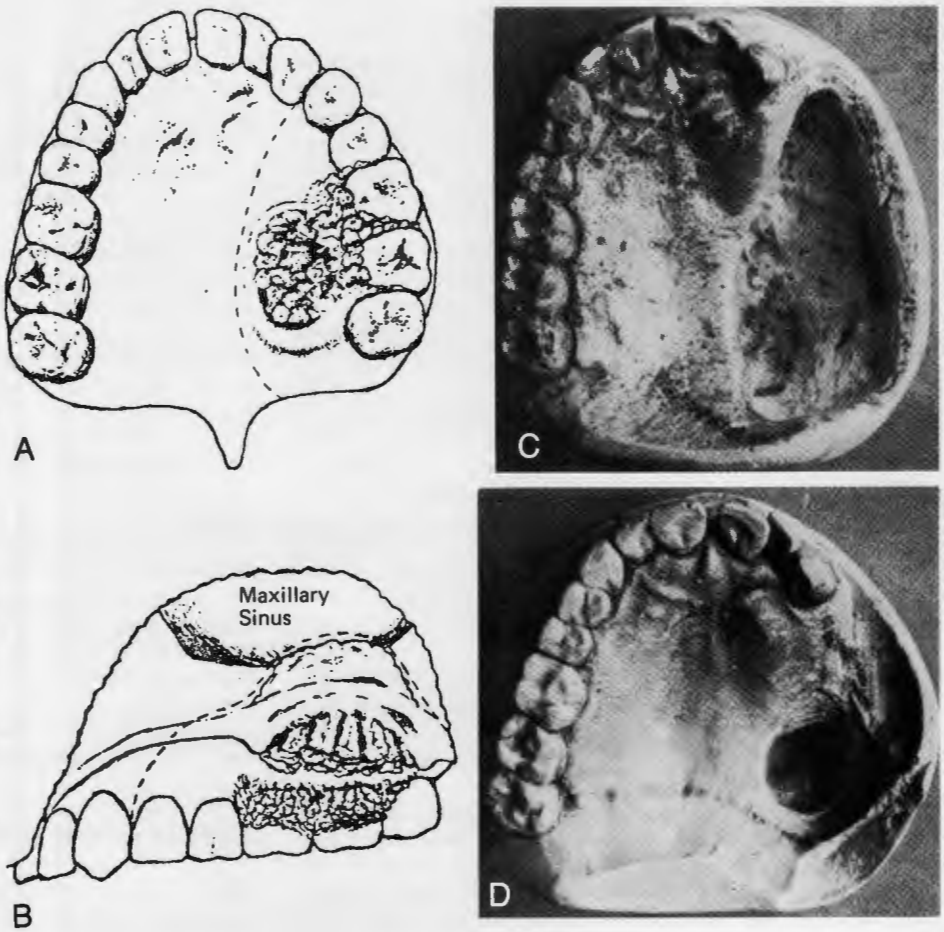

Figure 1-7. President Cleveland's tumor. *(A* and *B)* Sketches reconstructing Cleveland's tumor, based on descriptions by physicians who examined him. The dotted lines represent the extent of the surgery. *(C)* Cast of Cleveland's upper jaw made in July 1893 by prosthodontist Kasson C. Gibson. The defect measured 2½ × 13/16 inches. *(D)* Cast made 4 years later, in 1897, shows defect measuring only 11/16 inch × 7/16 inch. (*A* and *B* from Brooks JJ, Enterline HT, Aponte GE. The final diagnosis of President Cleveland's lesion. Trans Stud Coll Physicians Phila 1980;10:1–25, *C* and *D* from Morreels CL Jr. New historical information on the Cleveland operations. Surgery 1967;62:542–551)

publicity would jeopardize his management of the crisis.[88,120,147]

Bryant was a good choice for surgeon. He had previously presented a paper entitled "A History of Two Hundred and Fifty Cases of Excision of the Superior Maxilla" to the New York State Medical Society. Only two of the cases were from his own experience, but he was certainly familiar with the indications and risks of the operation. He reported a 14% mortality rate for the series.[23,122]

On June 30, the president left Washington and boarded a friend's yacht at New York City, purportedly for a vacation. In fact, Cleveland's physicians had made preparations to do the operation on board the yacht. In addition to O'Reilly and Bryant, the surgical team included John F. Erdmann, Bryant's surgical assistant; William W. Keen, a distinguished Philadelphia surgeon; Edward G. Janeway, a prominent New York internist; and Ferdinand Hasbrouck, a New York City dentist who was skilled in the use of nitrous oxide as an anesthetic.[13,122] The yacht's "saloon" had been fitted out as an operating room. The necessary drugs and gases had been brought aboard, as well as the surgical instruments and two storage batteries for an electric cautery and electric light. The crew was told that the president was having dental work done.

On July 1, the president's mouth and the surgeon's hands and instruments were thoroughly disinfected. The surgeons donned aprons over their street clothing. There was considerable worry about Cleveland's general medical condition. According to Keen, "Our anxiety related not so much to the operation itself as to the anesthetic and its possible dangers."[88] The 56-year-old president drank socially and smoked cigars heavily, was overweight, and had mild chronic nephritis, but, after a careful examination, Janeway pronounced him fit for the operation. Just after noon, as the yacht steamed toward Long Island Sound, the operation commenced. Bryant operated, with Erdmann and Keen assisting, while Janeway kept watch over the president's general condition. Anesthetics used in the course of the operation included cocaine, nitrous oxide, and ether, with the aim being to use ether as little as possible because of the president's potential medical problems. According to Keen, Hasbrouck extracted the two left upper bicuspid teeth, and the first incisions were made in the gum and hard palate.

> The entire left upper jaw was removed from the first bicuspid tooth to just beyond the last molar, and nearly up to the middle line. The floor of the orbit . . . [was] not removed. . . . A small portion of the soft palate was removed. This extensive operation was decided upon because we found that the antrum . . . [was] partly filled by a gelatinous mass. . . . The entire operation was done within the mouth, without any external incision, by means of a cheek retractor. . . .[88]

Bleeding was controlled by the electric cautery, pressure, hot water, and one ligature. The electric light was reported to have been very useful. The operation was completed before two o'clock, and the president's condition was very good.[122]

Cleveland was out of bed the second day after the operation, and, on July 5, was able to walk from the yacht when it arrived at his summer home, where he went into seclusion. His recovery was interrupted, however, when Bryant, who remained in attendance, decided that some "suspicious tissue" visible on the wound should be removed; Janeway, Keen, and Erdmann again boarded the yacht, where Bryant operated again on July 17, removing the suspicious tissue and recauterizing the entire surface of the wound.[88,122]

Thereafter, recovery was apparently smooth, although when the packing was removed from the wound, the president's speech was said to be "wholly unintelligible, resembling the worst imaginable case of cleft palate."[88] Kasson C. Gibson, a New York City prosthodontist, set up a dental laboratory in the president's summer home and fabricated a prosthesis of vulcanized rubber that was attached to a dental plate. On his original cast of Cleveland's upper jaw, in the possession of the New York Academy of Medicine, it can be seen that the original surgical defect measured about 2½ inches by 13/16 inch (see Fig.1-7*C*).[122] Suspicion had been aroused by the circumstances of the president's precipitate departure from Washington, and rumors soon spread that he was ill. His family and cabinet members specifically denied that the president had cancer.[88,122] Cleveland returned to Washington, and, on August 7, he addressed a special session of Congress. He was found to look and sound better than he had before leaving Washington, an improvement attributed to rest and sea air. The secret seemed safe.[122]

On August 29, however, a detailed and mostly factual account of the operation was published in the Philadelphia *Press*. Hasbrouck was the weak link in the conspiracy. His story was related to Elisha J. Edwards, a correspondent for the *Press*, and Hasbrouck confirmed it. The story was specifically and vigorously denied by everyone else involved in the case, even to the point of outright lies. The president's public appearance on August 7 with no scar on his face and no speech defect did much to discredit Edwards' story. The reporter's reputation suffered and was not restored until long after he and Cleveland both were dead.[75,88,120,122]

Cleveland's oral defect closed through the years. A cast taken by Gibson in 1897 shows it to be less than an inch in diameter (see Fig.1-7*D*).[122] Cleveland died in 1908, apparently the result of cardiovascular and renal disease and an intestinal blockage of uncertain origin.[18]

The story of Cleveland's illness was finally made public in 1917. Keen, then 80 years old and retired from practice, had kept a scrapbook of clippings, notes, and letters about the operation. He published the full story in a book entitled *The Surgical Operation on President Cleveland in 1893*[88] and in the *Saturday Evening Post*.[89,122]

Cleveland's physicians disagreed over the histology of the tumor, and all of the original pathology reports have apparently been lost. More than 80 years after the operation, in an effort to settle the question, samples of the tissue (preserved in the Mütter Museum of the College of Physicians of Philadelphia) were examined by modern pathologists. Their opinion was that the tumor was a verrucous carcinoma, accounting for the initial cauliflowerlike appearance described by O'Reilly, the differences of opinion regarding histology, and the lack of recurrence of the tumor in the 15 years that Cleveland lived after the operation.[18]

Cancer of the Larynx and Pharynx

The treatment of laryngeal and hypopharyngeal cancer was complicated by the fact that, although ancient phy-

sicians knew such tumors occurred, a technique for examining the larynx was not developed until the mid-19th century. Credit for the invention of mirror laryngoscopy is generally given to Manuel Garcia, whose description of his self-examination of his larynx expresses the spirit of scientific endeavor in the 19th century (or, indeed, in any century):

> I placed against the uvula the little mirror (which I had heated in warm water and carefully dried): then, flashing upon its surface with the hand mirror a ray of sunlight, I saw at once, to my great joy, the glottis wide open before me, and so fully exposed, that I could perceive a portion of the trachea. When my excitement had somewhat subsided, I began to examine what was passing before my eyes. The manner in which the glottis silently opened and shut, and moved in the act of phonation, filled me with wonder.[65]

Garcia was not really the first to use a mirror to visualize the larynx. For instance, in 1829, Benjamin Babington demonstrated a "glottiscope" with a single mirror on which sunlight was concentrated by means of a hand lens. The clumsy device included a built-in tongue depressor. Babington reportedly used his glottiscope for many years to examine patients, but no one else adopted his apparatus.[32,69,162]

Garcia was able to examine himself as he did because he was a trained singer and could consciously control his tongue and throat muscles. He was born into a family of professional musicians; his parents and his two sisters were famous opera singers. They were Spanish by nationality, but they toured Europe and America. His father established a voice training school in Paris, and, in about 1830, Manuel decided (because his voice was not good enough for an operatic career) to join his father in teaching. In the 19th-century manner, he was serious and scientific in pursuing his chosen profession. He studied in the Military Hospital of Paris for a year or two in an effort to learn all that medicine could teach him about the human voice. He also became thoroughly familiar with the anatomy of the larynx by dissecting many human and animal specimens at home. He published a paper in 1840 on the human voice, and later he published others on his methods of teaching singing. Perhaps his most famous pupil was Jenny Lind, the "Swedish Nightingale." He was not satisfied with these activities, however, as is clear from what he later said: "During all the years of study and investigation of the problems of voice production, one wish was ever uppermost in my mind—if only I could see the glottis."[148] In 1850, he was appointed professor at the Royal Academy of Music in London. Thereafter, England became his home, and it was to the Royal Society of England that he presented his discovery of mirror examination. It is typical, however, that his 1855 paper was not about laryngoscopy per se; it was, instead, a highly technical discussion on the production of voice—different from those that preceded it because he no longer had to theorize about the movements of the larynx that corresponded to various tones, since he could actually watch them being made.[32,64,90,148]

Garcia's report was met with apathy in England, but Ludwig Van Türck of Vienna worked on a similar device that made use of sunlight and a hand mirror during the summer of 1857, giving up in disgust when the cloudy days of autumn arrived. He gave one of his instruments to Johann Czermak of Budapest, who thought of having the examiner wear a perforated concave ophthalmoscopic mirror over his eye to gather and reflect a beam of artificial light. Czermak's idea really made routine laryngoscopy possible. He and Türck both took up laryngology with enthusiasm, later writing books disputing each other's claim of priority in the use of the laryngoscope. Morell Mackenzie, the first English laryngologist, learned the technique in Czermak's Budapest clinic in 1859. The first laryngoscopic mirror was introduced in New York in 1858, and, by 1861, a paper about laryngoscopy was read to the New York Academy of Medicine. Within a decade of Garcia's report, the technique of laryngoscopy was accepted, and laryngology was on its way to becoming an established specialty.[32]

Garcia continued his distinguished career as a teacher and voice specialist until he retired at the age of 96. In 1905, on the occasion of his 100th birthday, he was honored as the "father of laryngology" at a celebration in London arranged by Felix Semon, the dean of English laryngologists at the time. Whether or not Garcia may be said to have invented the technique of mirror laryngoscopy, he was the first to report his systematic observations of the larynx.[82,90,148] The early laryngologists, particularly Mackenzie in England, the German surgeon Viktor von Bruns, and Jacob D. Solis-Cohen of Philadelphia, became skilled in performing laryngeal treatment through the mouth.[33,162] A specialized set of surgical instruments was developed for such operations. Few malignant tumors could be treated successfully through the mouth, however. Thyrotomy, the exposure of the larynx by splitting the thyroid cartilage, had been described for the treatment of laryngeal polyps by the 18th-century Parisian surgeon, Pierre J. Desault, and, 100 years later, it was still sometimes called "Desault's operation."[49,141] After the introduction of anesthetics, thyrotomy, or laryngofissure, was performed more frequently for piecemeal removal of tumors followed by cauterization, often in cases much too advanced to be cured by this procedure. By 1868, there was disillusionment with thyrotomy because it was recognized that this procedure was inadequate in most cases of malignancy.[163]

At his clinic in Vienna, Billroth was at this time preparing to carry out total laryngectomy. Vincenz Czerny, then one of Billroth's surgical assistants, performed a series of successful laryngectomies on dogs and published the results in 1870. It became a question of waiting for the right patient, and he appeared in November 1873, a 36-year-old teacher of religion who had a biopsy-proven cancer beneath the true vocal cords. He had been treated through the mouth with cauterization and partial excision, but the tumor recurred, and it was decided that an "external operation" was the only hope for cure. Billroth first performed laryngofissure and removed the tumor with scissors and curet. The patient was soon found to have extensive recurrence. Billroth planned curettage of the entire larynx, but, during surgery on December 31, the tumor was found to be too extensive for this procedure to offer any hope of cure. The man was allowed to awaken, and his consent to total laryngectomy was obtained. Billroth performed the operation along the lines that Czerny's experiments had established. He had considerable difficulty controlling bleeding, but he managed to perform an extensive dissection that included the base of the epiglottis and the first two tracheal rings; he sutured the tracheal and pharyngeal openings to the skin and brought the edges of the esophagus together (Fig. 1-8). Four hours later, he had to

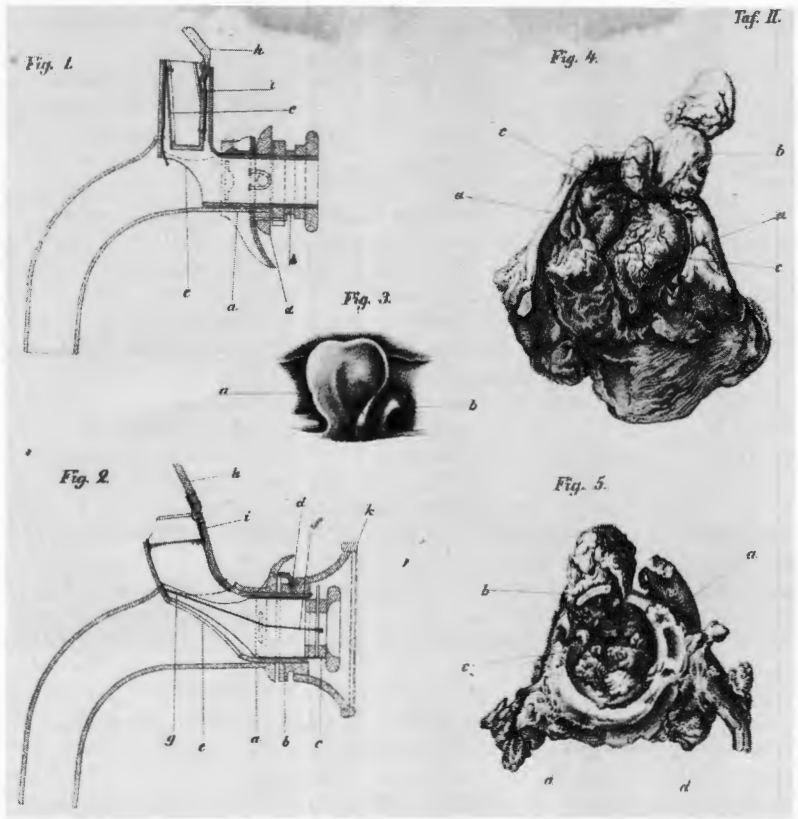

Figure 1-8. Plate illustrating Gussenbauer's report of Billroth's original laryngectomy. *Fig. 1* is the first artificial larynx Gussenbauer constructed. (a) Tracheal limb of tube. (b) Pharyngeal limb of tube. (c) This part shifts upward on phonation. The rotating ring (d) serves to fixate the tubes. The opening (e) communicates with the trachea. Plate (h) is kept open by a spring (i). The vibratory device quickly filled with mucus. *Fig. 2* is the improved version, which was quite successful. Letter designations are the same as in *Fig. 1*; in addition, f is the frame in which the metal vibrating tongue is fastened, and k is the respirator affixed to the pharyngeal tube. *Fig. 3* is the laryngoscopic view at the time of the patient's discharge. (a) Epiglottis. (b) Catheter introduced from below into the pharyngeal opening. *Fig. 4* is the excised larynx, from above. (a) Boundaries of laryngeal entrance. (b) Supraglottic extension of cancer. *Fig. 5* is the excised larynx, from below. (a) Cricoid cartilage. (b) Part of trachea. (c) Subglottic extension of cancer. (d) Mucous membrane not yet involved by cancer. (Gussenbauer C. Über die erste durch Th. Billroth am Menschen ausgeführte Kehlkopf-Exstirpation und die Anwendung eines künstlichen Kehlkopfes. Arch Klin Chir 1874;17:343–356)

reoperate to place ligatures to control bleeding from the left superior laryngeal artery. Amazingly, the patient did not develop any infection. The sutures and ligatures were removed after 3 days, leaving a midline wound, with the tracheal stoma below and the pharyngeal fistula above. The patient was fed by tube at first, but the pharyngeal fistula began to close, and he was able to swallow liquids on the 8th day after surgery and solids by the 18th day. Czerny and Karl Gussenbauer, another of Billroth's surgical assistants, had already done some work with dogs toward devising an artificial larynx, and Gussenbauer was assigned the task of helping the patient speak again. He was able to provide an artificial larynx that enabled the patient to speak loudly and clearly, but with a monotonous tone (see Fig. 1-8). The patient was discharged in March 1874, but he suffered local recurrence of the tumor and died later in the year.[2,48,72,156,173] The artificial larynx, which shunted air from the trachea to the pharynx, was based on the same principle as the modern-day Singer-Blom and Panje devices (see Chap. 19).

This was probably the first laryngectomy, and certainly it was the first performed for cancer. Despite the dangers of the operation, others followed in quick succession in Czechoslovakia, Poland, Germany, and Italy. The first total laryngectomy in the United States was performed in 1879. The patient survived the operation but committed suicide a week later. In 1883, Solis Cohen[152] published a collection of 65 laryngectomy case reports in which over one third of the patients mentioned had died within a month of the operation.

Treatment of laryngeal cancer became the subject of international controversy, in both medical and lay publications, when Prince Frederick, the middle-aged crown prince of Germany, developed a laryngeal lesion in March 1887. It was first treated with cauterization through the mouth, but it quickly regrew. By May, the tumor was distinctly larger than ever and the mobility of the vocal cords was lessened. A laryngotomy was recommended for direct visualization of the tumor and, if possible, removal. It was decided, however, to request one more expert consultation, and (at the behest of the crown princess, eldest daughter of Queen Victoria of England) the English laryngologist, Morell Mackenzie, was summoned. Mackenzie disagreed with the conclusion of the German physicians, contending that there should be proof that the condition was malignant before a major operation was undertaken. He recommended biopsy, which was done three times during May and June. The specimens were submitted to Virchow, who was a friend and admirer of the crown prince and who reported that they showed no evidence of malignancy.[104] To the despair of the German physicians, only minimal transoral treatment was carried out, despite the malignant behavior of the lesion, until November, by which time the tumor had grown to such an extent that only a total laryngectomy with its high risk of operative mortality held any possibility of success (Fig. 1-9). Prince Frederick decided against it. In February 1888, he underwent a tracheotomy to relieve stridor. Carcinoma was diagnosed in March by Wilhelm Waldeyer based on sputum specimens. Frederick lived long enough to succeed to the throne on March 9, but he died on June 15. At the autopsy, the last he ever performed, Virchow found laryngeal carcinoma with metastases in cervical lymph nodes. The crown passed to Frederick's militant son, the Emperor William II, who led Germany into World War I. Whether his peace-loving father could have prevented this conflict can only be a subject for speculation. The

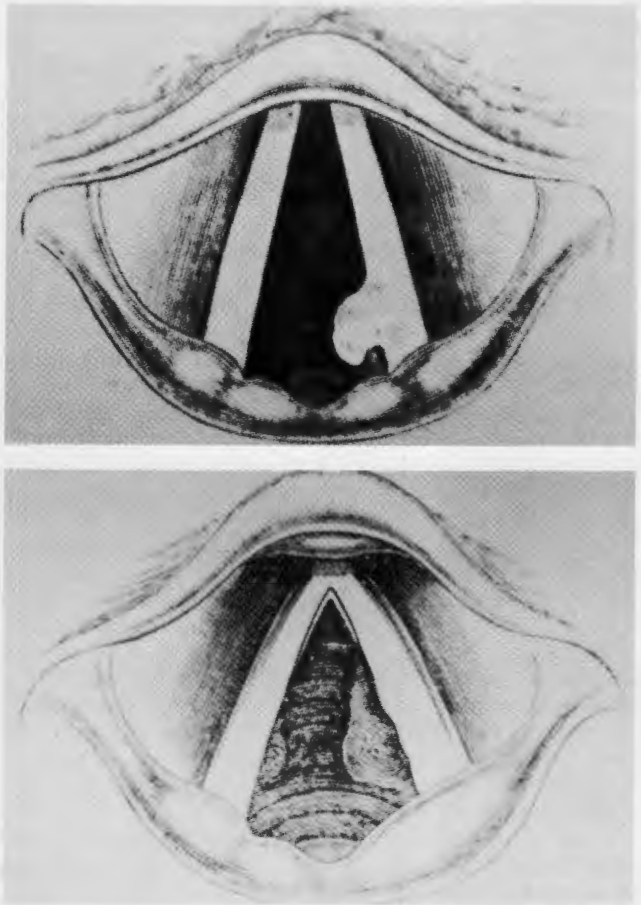

Figure 1-9. Drawings by Morrell Mackenzie of the laryngoscopic appearance of Crown Prince Frederick's laryngeal tumor, published in his 1888 book, *The Fatal Illness of Frederick the Noble*. (*Top*) Representation of the initial examination in May 1887. (*Bottom*) Drawing of the Prince's condition in November 1887, when Mackenzie had to admit that the tumor was probably malignant. (Gerlings PG. Laryngeal carcinoma: some considerations with reference to the illness of Emperor Frederick III. Eye Ear Nose Throat Monthly 1968;47:566–571)

medical repercussions were also felt for some years, particularly the question of whether biopsy should or should not be carried out before treatment in cases of laryngeal disease. An acrimonious and undignified dispute was carried out in print between the German physicians and Mackenzie on this and the other disputed points in the case, beginning even before their royal patient's death. Mackenzie died with his reputation marred by this episode, although later writers have been more balanced in their judgment of his career.[30,66,107,111,121,125,126,164]

The results of laryngectomy were greatly improved by the technique developed by Glück in Germany in 1881 and by Solis Cohen in the United States whereby the trachea and larynx were elevated above the level of the wound, preventing the entry of blood into the lungs during the procedure, and the hypopharyngeal defect was closed, lessening the risk of postoperative aspiration.[33,163] In 1913, Glück and Soerensen reported that only 22 of 244 patients had died intraoperatively and that 24 patients had survived 4 to 15 years after total laryngectomy for carcinoma of the larynx. It should be noted that these were more advanced cases; they performed thyrotomy or hemilaryngectomy in less advanced cases, with excellent results. The value of laryngectomy was still widely disputed.[43,141]

Later Surgical Developments

Technical improvements in the surgical techniques for head and neck cancer operations came rapidly and included improved methods of producing anesthesia, the development of specialized instruments, and refinements of the operative method. However, dramatic lowering of operative mortality depended mostly on meticulous preoperative and postoperative care of the patient, techniques for which were developed by Chevalier Jackson of Philadelphia, George W. Crile of Cleveland, and John E. MacKenty of New York, among many others. In this preantibiotic era, precautions taken before, during, and after surgery to lessen the infection rate were of crucial importance. Postoperative care included nasogastric tube feeding and elaborate care to prevent or treat aspiration. Statistics were also improved by more knowledgeable selection of patients for the operations.[84,103] In the mid-20th century, the list of supportive measures grew with the discovery of antibiotics, the use of blood transfusions, a better understanding of blood chemistry, and still further improvements in anesthetics and in operative and rehabilitative techniques.[141]

Surgeons could focus on their actual goal—control of the cancer—once patients began routinely to survive the operative procedures. It had long been recognized that control of the primary tumor was not enough, in many cases, to cure the patient of cancer. Early attempts to cope surgically with neck lymph node metastases reached a culmination in 1906 when Crile, after the model of Halsted's treatment of breast cancer, advocated en bloc resection of the "entire lymphatic-bearing tissue" in the neck, on one or both sides, for patients with a wide variety of head and neck tumors when the neck nodes were enlarged. A less radical block excision of the pertinent lymphatic drainage area was advised when there was no palpable neck disease present.[40]

The English surgeon, Wilfred Trotter, established the modern system for naming, diagnosing, and treating pharyngeal cancers on the basis of the natural history of the tumors.[178] Writing in 1913, he described the manifestations of and the best therapy for tumors of each of five anatomic areas: nasopharynx, oropharynx, epilarynx, pyriform sinus, and hypopharynx.[167] He said that neck nodes were characteristic for nasopharyngeal tumors, and the presentation of hearing loss, trigeminal pain, and partial paralysis of the palate (which he described in 1911) is still known as "Trotter's triad."[166,178] He said that these tumors were frequently "endotheliomata of a peculiar and characteristic type," which were found also at times in the tonsil and occurred mostly in young males (probably this category included lymphoepithelioma, not described until 1921).[167] For nasopharynx tumors, curative treatment was generally not possible. Tumors of the oropharynx, including the tonsil, the anterior tonsillar pillar, and the base of the tongue, showed a "marked tendency to longitudinal spread [which] renders free longitudinal exposure an essential necessity in the operative technique."[167] Cancer of the base of the tongue was particularly serious because of "the remarkable tendency it has to grow into the substance of the

tongue without in the early stages ulceration or projection at the surface" and because it produced few early symptoms and resulted in presentation at an advanced stage.[167] The epilaryngeal tumors were those referred to by others as "extrinsic tumors of the larynx," which arose on the epiglottis or aryepiglottic fold. Unlike others, Trotter found that these lesions were "the most hopeful of all malignant pharyngeal tumors" because of their tendency to produce symptoms at an early stage; he thought that total laryngectomy was often unnecessary in treating them.[167] In the case of tumors of the pyriform sinus, however, he could only be pessimistic. Its depths were, according to him, "quite inaccessible to laryngoscopic examination."[167] The tumors produced no early symptoms and often presented as "obviously malignant glands in the neck without ostensible primary tumour."[167] This was the only pharyngeal tumor, in his experience, for which "that terrible operation," a total laryngectomy, was always required, because it was always advanced at the time of the operation.[167] He found that early diagnosis was possible for hypopharyngeal carcinomas, but that treatment was frequently delayed because of the mistaken belief that the tumors were inoperable. He also noted that, although most other pharyngeal tumors occurred mostly in men, hypopharyngeal cancers occurred more frequently in women. As to treatment, Trotter recommended "lateral pharyngotomy by the transthyroid route," as he termed it in a later (1920) paper, to provide the necessary "free and untroubled access to the part."[168] He advised excising a ½-inch margin for early tumors and a 3/4-inch to 1-inch margin for moderately advanced cases, with a larger margin in the direction in which the tumor was known to have a propensity to spread. Margins were to be determined by pathologic examination rather than by anatomy. As for treatment of the neck, he attributed to the otolaryngologist, Henry Butlin, the rule that "the gland operation should be as much a part of the treatment as the removal of the primary growth."[167] If there were few or no palpable neck metastases, the operation was limited to removal of "all lymphoid tissue" above the thyroid cartilage, but it was extended horizontally "to comprise about four fifths of the circumference of the neck."[167] If there was extensive lymph node involvement, the operation was unilateral, but its course extended downward and included the sacrifice of the spinal accessory nerve, the sternocleidomastoid muscle, and the jugular vein.[167]

The increasingly radical efforts of the early 20th-century surgeons to cure patients of head and neck cancers sometimes produced the unhappy result of a patient without recurrence of cancer who was so maimed by the treatment that his extended life span was miserable in quality. The cartoon character "Andy Gump" was probably based on a real man, a patient treated by radical surgery for lip cancer at John Hopkins in 1915, who lived in upstate New York in the same small town where cartoonist Sidney Smith lived as a boy. Andy Gump was depicted as having no lower jaw, a defect that caused him no apparent disability and produced only a comic disfigurement; the reality, of course, was grim. An unsuccessful lawsuit filed by the cured patient in 1928 charged that the cartoonist had disgraced and humiliated him, but it would be fairer to say that the lifesaving surgery had caused his problems.[154]

Plastic surgeons and prosthodontists developed new techniques and materials in their efforts to repair the mutilations of war. The early work on skin grafting by Reverdin, Ollier, and Thiersch was done around the time of the Franco-Prussian War (1870 to 1871), but, before World War I, there was really no specialty of plastic surgery. This war offered ample work to those interested in reconstructive operations.[110] As the Dutch oral surgeon, Johannes Esser, put it in his 1917 paper, "As I made in Austria over 700 plastic operations on war-cripples I enlarged my practical experience, especially in repairing defects of the face in an important manner."[55] He described the neck and cheek flap, centered on the external maxillary artery, for reconstruction of upper lip and cheek defects; the nasolabial flap for lower lip defects; and the use of a mold of Stent's dental compound, wrapped in a "Thiersch graft" raw side out, to hold the graft in place in a cavity. He noted that plastic operations should leave neither uncovered tissue nor excess skin folds, for "a beautiful plastic is always a mathematically correct and maximally economical one."[55] Harold E. Gillies did his first plastic surgery on British troops in World War I and later went on to establish the specialty of plastic surgery in England. He described the many uses he had found for the tubed pedicle flap in his textbook, *Plastic Surgery of the Face,* published in 1920. Vilray P. Blair, already known as a reconstructive surgeon before the war, led the American section on oral and plastic surgery. He later developed the method of raising large flaps, described in his "The Delayed Transfer of Long Pedicle Flaps" in 1921, and he described the use of the larger, thicker split-thickness skin graft in 1929. In 1938, the invention of the dermatome by Earl C. Padgett made it easier to obtain skin grafts, just in time for use in World War II.[35] These new techniques could often be applied to the rehabilitation of cancer patients after radical surgery. In the 1950s, Vahram Bakamjian, of Roswell Park, raised a tube flap from the cervical area to repair the defect left by radical cancer surgery and used the pectoral flap to cover the wound in the neck.[11,12]

Sigmund Freud suffered and eventually died from a carcinoma of the hard palate, diagnosed in 1923 when Freud was 67 years old. He underwent a total of 33 operations and numerous x-ray and radium treatments for his disease. Freud's biographer, Ernest Jones, published a translation of the case notes of Hans Pichler, the distinguished Viennese oral surgeon who cared for Freud from the first radical operation for recurrence in 1923 until Freud left Vienna in 1938 for England as a refugee from Nazism.[139] In October 1923, Pichler described "a crater-shaped typical ulcer at the posterior part of the [maxillary tuberosity] with slight infiltration into the palatoglossal fold continuing into the buccal mucous membrane and over the margin of the mandible."[85] Pichler first performed "typical clearance of the submaxillary glands" and ligature of the external carotid artery on October 4. Some of the lymph nodes appeared "suspicious," but no malignancy was found microscopically. On October 11, Pichler resected the maxilla and part of the ascending mandibular ramus on the right side. The soft palate was mostly preserved, and the wound was covered by a "Thiersch-graft" taken from the left upper arm. A preliminary prosthesis was put in place at the time of the operation. After receiving the pathologist's report, Pichler immediately reoperated, cutting an additional 1½-cm margin in the soft palate and removing the pterygoid process, until the margins again appeared clear.[85]

For the remaining 16 years of his life, Freud struggled with his prosthesis, which he dubbed "the monster." He

had great difficulty inserting and removing it, owing in part to its large size and in part to trismus dating from his initial operation. He was in pain much of the time, and his speech was always more or less defective; he never again gave lectures. Despite frequent construction of new prostheses and adjustments of old ones, his prosthesis almost never fit properly, not too surprising in view of the constant threat of recurrence, with repeated operations and radiation treatments* and the subsequent postsurgical, postirradiation changes in his tissues. In addition, he had always had sinusitis off and on, and this problem continued. Despite all this, Pichler paradoxically concluded, on July 5, 1925, that the psychiatrist's problems with his prosthesis were "mainly nervous." Freud continued to work during these years, teaching, seeing patients, and writing, as much as his illness allowed. Definite tumor recurrence was diagnosed in 1936, and, finally, in May 1939, in London, a tumor was found "high above in antrum," and it was noted that "Operation not indicated any more." Some additional radiation treatments were given, and Freud survived until September.[41,85]

RADIATION THERAPY IN HEAD AND NECK CANCER

Early X-Ray Therapy

In January 1896, Röntgen's discovery of x-rays was publicized throughout the world. The medical usefulness of the new rays was immediately obvious, and the March 1896 issue of *Index Medicus* listed more than 40 published papers dealing with the subject. As soon as the effects of the rays on tissues were observed, x-ray treatment of cancer was tried, and head and neck cancers were among the first to be treated. In fact, on February 3, 1896, Voight reported to the Medical Society of Hamburg that he had irradiated a case of pharyngeal cancer and that the patient's pain had been relieved. For this effect to have occurred by February 3, the treatments were probably administered sometime in January.[29,171]

Emil Grubbé, of Chicago, administered x-ray therapy to a patient with breast cancer on January 29, 1896, making him the first in the United States to administer radiotherapy. He and his partner, Albert Schmidt, a German glassblower, had been producing vacuum tubes, mostly electric light bulbs but also Geissler tubes and a small mica-vane radiometer tube. Grubbé was a freshman medical student (and teacher of physics and chemistry) at Hahnemann Medical College of Homeopathy in 1896 when Röntgen's discovery was reported. He claimed that he experimented with cathode-ray tubes and that he tested them by watching the image of his hand on a fluoroscopic screen.[77] As Hodges[77] recounted in his biography:

> Toward the end of January, 1896, Emil noticed severe itching on the back of the left hand followed shortly by swelling, inflammation, pain, blistering, loss of hair (epilation), and eventually breaking down of the skin (desquamation). That was the state of affairs, he says, when on January 27, 1896, he attended a faculty meeting of the medical college where he was both student and teacher. Several of his physician colleagues and teachers, noticing that his hand was bandaged, inquired about it and when the bandage had been removed offered therapeutic suggestions. One of the group, Dr. J. E. Gilman, instead of advising as to treatment expressed the belief that if x-rays could be so damaging to normal tissues they might be effective against disease tissues such as neoplasm. This idea impressed the other physicians who were present and two of them offered to send Emil cancer patients if he cared to make a therapeutic trial. In this manner, the ground was laid for the birth of radiation therapy.
>
> At 10:00 a.m., on Wednesday, January 29, 1896, Mrs. Rose Lee, a patient of Dr. R. Ludlam, came to Emil's little place at 12 Pacific Avenue and he administered the first of eighteen treatments to a carcinoma of her left breast which had recurred after a first and then a second operation. The treatment reduced her pain, but she died about a month after the first visit.

Grubbé was kept busy treating patients for cancer and other diseases while he completed his medical education, and he had a long career in radiology. Like many of the pioneers in the field, he developed radiation-induced skin cancers that caused him great suffering, although he survived to be 85 years old. He was concerned late in his life with the question of priority in the use of radiation therapy, and he willed his fortune to the University of Chicago on the condition that a biography be written, which he hoped would document his claims. This task was carried out with sympathy, skill, and a strict regard for the truth by Paul C. Hodges,† and the resulting biography, *The Life and Times of Emil H. Grubbé*, makes fascinating reading for anyone interested in the early days of radiology.[77]

As the effects of radiation on skin were recognized, many dermatologists experimented with the new treatment medium (Fig. 1-10). At the 1902 meeting of the American Medical Association Section of Cutaneous Medicine and Surgery, the use of x-rays was reported for a variety of skin conditions, ranging from acne and eczema to lupus and cutaneous tuberculosis, as well as for cancers.[165] The fact that radiation would cause hair to fall out was discovered in 1896 and led to its widespread use for epilation in cases of ringworm of the scalp.

* Freud's radiation therapist early in the course of his disease was Guido Holzknecht, of whom Jones[85] writes: "Holzknecht, who had been a former patient of Freud's, was the leading radiologist in Vienna and one of the pioneers of that science. Like so many of those pioneers he was also a victim and was now [in 1931] in hospital dying of cancer, which an amputation of his right arm had failed to arrest; he died a few months later. Freud and Schur [Dr. Max Schur, Freud's internist] visited him, none of them being under any illusion, and when they parted Freud said, 'You are to be admired for the way you bear your fate.' Holzknecht replied, 'You know I have only you to thank for that.'"

† Before the cumulative long-term effects of radiation were widely known, the early radiologists often calibrated their machines on themselves. Dr. Hodges, who was a radiologist in Peking, China, from 1919 to 1927, calibrated his machines on his own legs, which many years later showed numerous round, depressed scars (the size and appearance of cigarette burns) resulting from this technique. Many early radiologists died as a result of radiation-induced cancers of the skin or soft tissues, leukemia, or aplastic anemia[78] (Hodges PC, personal communication, 1982).

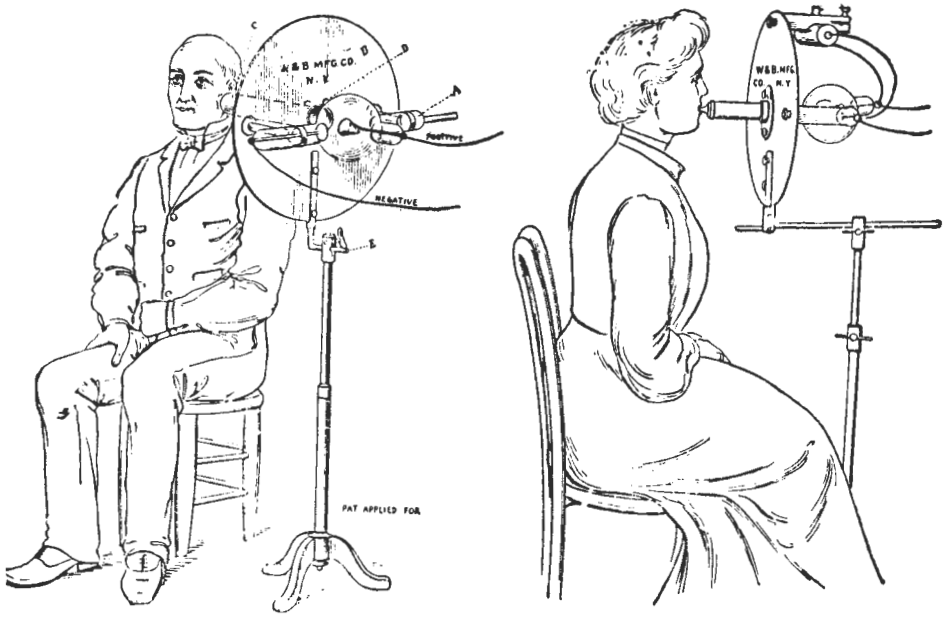

Figure 1-10. Treatment of facial skin and intraoral cancer with an x-ray tube mounted behind an "Allen shield," illustrated by dermatologist Charles W. Allen of New York in his 1904 radiation therapy textbook. He reported that he had used this apparatus "constantly for about two years with much satisfaction. It is a great saving of time, as the patient has only to sit before the opening in the disk, and is also saved the discomfort of a mask or metallic covering to the body. . . . Treatment can be applied to any area in any position of patient." While cautioning that "we cannot to-day rely fully upon the ray alone," he was nevertheless enthusiastic about the results of x-ray treatment: "Let not the man arise who will cry, 'Away with x-ray for inoperable cancer!' until he can proclaim a nearer approach to a cure." (Allen CW. Radiotherapy and phototherapy including radium and high frequency currents, their medical and surgical applications in diagnosis and treatment. New York, Lea Brothers, 1904:103)

Skin cancers were an obvious target for radiation therapy, and two Swedish physicians, general practitioners in Stockholm, successfully treated facial skin cancers in 1899. Tage Sjögren treated a patient with basal cell carcinoma of the left lower eyelid and cheek with a total of one hundred 10-minute exposures over several months, producing total regression of the tumor but also producing a late dermatitis on the eyelid that resulted in ectropion of the lower lid.[62] Tor Stenbeck treated a woman with basal cell carcinoma of the nose with 99 treatments beginning July 4, 1899, and extending over several months. The patient was presented to the Swedish Society of Medicine in December 1899 and was presented to the Second International Congress of Radiologists in Stockholm in 1928, having survived nearly 30 years after treatment.[16] By 1904, the author of one early textbook of radiology commented that "the treatment of external forms of carcinoma, including those of breast, tongue, and cervix uteri, by the roentgen rays has become a recognized method."[14]

In September 1902, William Scheppegrell, a New Orleans otolaryngologist, reported his experience with the use of x-ray treatment for larynx cancer to the American Electrotherapeutic Association. The patient was a 57-year-old lawyer from western Louisiana who had suffered hoarseness for 6 months before consulting Scheppegrell in April 1902. He was found to have a tumor of the left side of the larynx with paresis of the left vocal cord. The patient had just been injured in a street accident while on his way to see Scheppegrell and had to recuperate before his cancer could be treated. In June, he returned, and the tumor had grown to the point that respiration was impeded, the vocal cord was paralyzed, ulceration had set in, and his voice was reduced to a husky whisper. To Scheppegrell's experienced eye, the lesion appeared to be a typical carcinoma of the intrinsic larynx. There was as yet no evident lymph node involvement. The patient was offered "laryngotomy" as treatment, but he declined the operation. Scheppegrell had used x-rays to treat laryngeal tuberculosis with good results and proposed that this treatment be tried, warning the patient that x-rays had been proven effective only in superficial carcinomas. The patient agreed to a trial of treatment. Scheppegrell used a high-tension Tesla coil to generate the current, and he decided to use a tube with medium vacuum, providing more penetration than was needed to treat superficial disease but less than that required for chest examination. In what was certainly one of the first references to elective node irradiation, he said "The face and chest of the patient were protected with specially prepared paraffin paper, no effort being made to limit the rays to the diseased area by means of lead foil. The object was to utilize the effects of the treatment on the neighboring tissues and on the lymphatic glands, in case these had been involved in the malignant process."[142] The patient was seated with his head bent back to expose the neck as thoroughly as possible to the x-rays. He had a 10-minute exposure every day for 20 days, with little apparent result except decrease in pain. He was sent home to await results before deciding whether to continue the treatment. Six days later, Scheppegrell was discouraged when he received a letter from the pa-

tient's wife, reporting that he was feverish, in pain, and expectorating blood clots. However, when the patient returned on July 24, Scheppegrell found the result to be almost incredible. Most of the tumor had disappeared, taking with it a large part of the left vocal cord. The patient's acute illness had apparently resulted from the sloughing process. X-ray treatment was recommenced and was continued for an additional 10 days, at which time the ulceration in the larynx had completely healed and the patient was sent home. Scheppegrell published the case in the New York Medical Journal (as well as in the British and French literature) with follow-up as of October 25, 1902, at which time the patient was in excellent condition with no evidence of recurrence. His voice had improved, and he had resumed his law practice.[142–144] Unfortunately, when Charles Allen (a New York dermatologist) cited the case in his 1904 radiotherapy textbook, he added, "This patient, I am informed, subsequently died from the disease."[7]

Leonard Dobson, of London, reported a case of advanced larynx cancer treated by radiation during 1901 and 1902. The tumor initially involved the neck lymph nodes and was considered to be too advanced for an operation. By October 1901, the patient, a 64-year-old man, could not speak above a whisper and required tracheostomy for dyspnea. He was weak and cachectic. As a desperation measure, x-ray treatments were begun. The report is vague as to the details of the treatment, but apparently the patient received daily 5-minute exposures over the course of several months. The neck nodes all but disappeared, and the primary tumor decreased greatly in size. The patient could talk again and take long walks. In June 1902, treatments were temporarily discontinued because he suddenly developed a severe skin reaction; they were resumed after the skin healed, and the tumor continued to shrink. Although treatments were reduced to 3-minute sessions three times a week, soon "the skin again gave way."[47] At this time, it was decided to switch to "electrotherapy" using high-frequency current. X-rays were tried again from time to time, but "one short exposure even was sufficient to create an angry blush of the skin."[47] The patient remained well until the autumn of 1902, when "a small abscess formed and burst at the side of the tracheotomy wound, leaving a fistulous track which never afterwards completely healed."[47] About November 1902, the tumor began to grow again, and, by March 1903, it was noted to have regained its original size. The patient went slowly downhill. Finally, "the whole right side of the neck necrosed," and he died of hemorrhage in August 1903.[47] Dobson noted that, although ultimately the patient had died, his life was much longer and better in quality than seemed possible when the x-ray treatments were started.[47]

The radiation sources available at this time produced large amounts of "soft" radiation, automatically producing a proportionately greater effect on the skin and superficial tissues. Some early therapists attempted to avoid severe radiation reactions by giving extremely cautious doses over a prolonged period of time, as in the Swedish skin cases. Other early therapists assumed that the immediate effects of radiation, those that are now considered acute side effects, were the important ones—they thought the tumor would burn up as if cauterized or would necrotize and slough as if resected.[24] To maximize such a result, these therapists emphasized applying the largest possible dose in the shortest possible time.

There was initially no way to measure the radiation being applied or to predict its effect on the patient. In 1902, Guido Holzknecht of Vienna developed a "pastille radiometer," based on the observation that certain chemicals would change color after exposure to roentgen rays. His initial "chromoradiometer" was not successful, but, by 1910, he had developed a system that consisted of a 4½-inch-long celluloid band that was colorless at one end and shaded through orange to deep brown at the other, which was compared to an exposed pastille to determine the radiation dosage (the darker the color of the exposed pastille, the higher the dose). The deepest color indicated an "epilation dose" when the pastille was placed halfway between the skin and the source of radiation. If the pastille was placed directly on the skin, the measured dose was only about one fourth as great, so higher doses could be measured. The reading had to be taken less than 1 minute after the radiation exposure because the color faded rapidly.[134] The system was inexact and subjective, but, according to Quimby, it was the best available at the time. The only alternative was still more subjective: direct observation of the effects of radiation on the skin. This was expressed in terms of the "erythema dose," the amount of radiation required to produce reddening of the skin when given in a single dose. The amount of radiation required to produce this effect would vary, of course, from patient to patient and from one radiation source to another, but the concept of the erythema dose was widely used nevertheless.

Considering the indeterminate amount and quality of radiation produced by the early tubes and the general ignorance of the biologic effects of radiation, it is little wonder that massive, sometimes fatal necrosis of soft tissue, bone, and cartilage often occurred in the first patients treated for head and neck cancer. At the same time, because only the superficial tissues were receiving tumoricidal doses of radiation, cancer cures were few. Probably only skin cancers or other superficial malignancies were actually cured in the earliest period of therapy development, although radiation was tried on almost everything, malignant or otherwise.

The more extensive tumors, especially those extending into deeper tissues, would show a good apparent response but would come back. As James Ewing later commented, "This fact proved most disconcerting, and I well remember my own feeling of amazement and incredulity upon finding that a tumor process once caused to regress and apparently disappear could start to grow again from the remnants of damaged cells."[56] In the same vein, commenting in 1936 on the high doses needed to cure carcinoma, Paterson said, "Doses slightly short of these figures produce an effect for which a very expressive name would be 'disappearance dose.' This consists of complete resolution in the first instance, very pleasing at first sight, but not permanent."[129] By 1910, there was disillusionment with the new modality, and it was feared that its uses as a curative agent were strictly limited.

Early Radium Therapy

One way around the limitations of superficial treatment was to try to place the radiation source directly onto the tumor, either by inserting it into a body cavity or by surgically exposing the tumor. X-ray tubes were awkward to use in this way, and "curie therapy" using natural radiation sources was begun soon after radium was

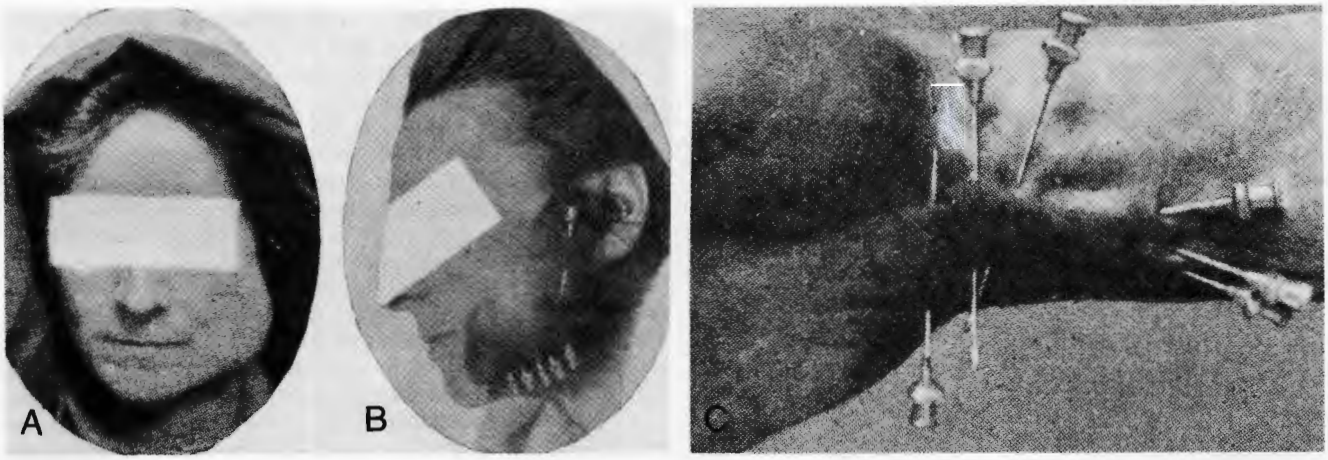

Figure 1-11. One of the first interstitial "radium emanation" needle implants reported by Walter C. Stevenson, of Dublin, was in a case of resectable "mixed parotid sarcoma." (*A*) Before treatment, the tumor was fixed and the patient had severe trismus. (*B*) Placement of the needles for the third implantation. Needles, containing varying amounts of radon, were left in place for 1 to 2½ days. According to Lederman, patients went home after the needles were inserted and returned for their removal.[96] After four implants, 7 weeks from the start of treatment, the tumor was much smaller and no longer fixed, and the patient could open her mouth. (*C*) The needles can be seen in more detail in a photograph of the implant of a painful fibrous scar of the wrist. (Stevenson WC. Preliminary clinical report of a new and economical method of radium therapy by means of emanation needles. Br Med J 1914;2:9–10)

discovered in 1898 by the Curies. The biologic effects of radium exposure were discovered inadvertently by Becquerel in 1901, when he left a tube of radium in his vest pocket for several hours. Fourteen days later, a reaction occurred on the underlying skin. Pierre Curie realized the possible medical value of radium and gave some to a Paris physician for experimentation. Only minute amounts of radium were available, but radium therapy was reported in Paris in 1901, in the United States in 1903, and Germany, England, and Russia in 1904. For head and neck cancer, applicators consisting of tubes containing radium salts (perhaps 25 mg of radium in one or two tubes) were inserted into the mouth or (as suggested by Alexander Graham Bell in 1903[153]) buried in tumors. Perhaps the best of these early applicators was reported in 1908 by Henri Dominici, of the Radium Institute of Paris. The "Dominici tube" enclosed the radium in platinum, which filtered out much of the less energetic radiation and thus decreased the side effects of treatment. Walter C. Stevenson, of Dublin, devised the method of sealing "radium emanation," radon gas, in tiny capillary tubes that could be loaded into hollow needles and inserted into a tumor, distributing the dose of radiation much more evenly than was possible by any other method. Stevenson reported good results in cases of parotid cancer, cancer of the floor of the mouth, and "malignant glands of the neck," among others (Fig. 1-11). This method, first used in 1914, was the forerunner of modern interstitial therapy.[96,157]

Many of the early experimenters with curie therapy were surgeons. In the United States, Robert Abbe, better known as a pioneer plastic surgeon (creator of the Abbe flap), began the use of radium in the treatment of head and neck cancer at St. Luke's Hospital in New York in 1903.[1] In 1912, Henry H. Janeway was appointed chief of cancer surgery and radiation therapy at Memorial Hospital in New York. Janeway was motivated in his radical experimentation partially by the fact that he himself suffered from ameloblastoma of the mandible, which was first diagnosed in 1905, was operated on many times, and was treated with various types of radiation therapy before finally causing his death in 1921.[56] Among other techniques, Janeway treated his patients with glass capillary seeds containing radon, which he distributed into the tumors. The radiation was essentially unfiltered and caused severe reactions, although, as Ewing stated, "If the patient could stand the ordeal, he was often rewarded by an unexpected cure of extensive disease."[56] Janeway was able to report cures of lip, tongue, and tonsil cancers using this method.

> All cases of carcinoma of lip, tongue, tonsil, skin, in his service were immediately assigned to radiation therapy. . . . The radical nature of this step may be revealed by the fact that the first cases of lip cancer treated by interstitial irradiation were done surreptitiously and the cases were exhibited only after all traces of the disease had disappeared, and all protests were throttled.[56]

Gioacchino Failla, Janeway's radiation research chief at Memorial after 1915, developed gold casing for the radon seeds in 1924 (only one of Failla's many contributions to clinical radiation physics through the years). Because the gold covering filtered out most of the beta radiation, these seeds produced fewer side effects and were used in the treatment of head and neck tumors for many years.[57]

The Beginnings of Modern Radiation Therapy

The development of x-ray therapy was left primarily to the radiologists. As Ewing[56] expressed it:

> The atmosphere of roentgen therapy was obnoxious to conservative minds. The noisy racket of the transformer, the noxious gases exhaled from the tubes in ill-ventilated rooms, and the retching of nauseated patients, created a repulsive contrast to the solemn ceremonies of the surgical amphitheater. . . . All one could really do was to place the patient under the machine and hope for the best.

Physicists attempted to develop objective means for measuring radiation output. After the more reliable Coolidge tube was introduced in 1913, it was feasible to express radiation output in terms of the known milliamperage and kilovoltage of the tube, and, by adding the factors of exposure time and source-to-skin distance to the equation, a dose could be calculated (eg, skin dose) for any given beam. This formula was developed enough by 1927 that Mackee could publish a set of dose tables, and his technique of dose prescription was used, particularly by dermatologists, for many years.[134]

The ionization effect of radiation was recognized by Röntgen only a few weeks after he discovered x-rays, and this effect was used along with the other methods mentioned above to measure radiation. In 1914, Szilard detailed the requirements for a practical, objective radiation meter and described an ionization chamber that was the forerunner of modern instruments. An internationally recognized radiation unit, the roentgen, was defined and adopted in 1928.[134]

Claudius Regaud, head of the radiobiologic laboratory of the Radium Institute in Paris, began after World War I to study the effects of x-rays in animals. He found that it was impossible to sterilize the testicles of a ram or rabbit with a single dose of radiation without causing extensive tissue destruction, but, if the dose was divided into several fractions, sterilization could be achieved without serious tissue damage. Regaud theorized that the rapidly dividing testicular cells might be analogous to cancer cells, and, on this basis, Henri Coutard began treating head and neck cancers at the Institute with fractionated doses of x-rays in 1919. This work was the foundation of modern external-beam radiation therapy.[87] Carcinomas of the larynx and hypopharynx were, as Fletcher says, "the first deep-rooted tumors to be cured by fractionated external irradiation."[59] After careful experimentation with varying dosage schedules, Coutard concluded that the best results were obtained by repeating small doses of radiation daily for several weeks. The x-ray machines he used were so low in output that each patient was treated for at least 50 minutes a day, ranging up to periods of 3 to 4 hours a day that were divided into a morning and an afternoon session. Treatments were administered 7 days a week, with occasional days of rest if the treatment continued for more than 25 days. The best results were obtained when he treated patients with cancer of the tonsillar region for 30 to 40 days; patients with cancer of the lower pharynx for 24 to 31 days; and patients with cancer of the larynx for 15 to 21 days. In general, smaller tumors could be given lower total doses over shorter periods, whereas larger treatment fields required higher doses over lengthier periods. Coutard used some of the early dosimeters—in 1932, he mentioned both "ionometric apparatus" and the "colorimetric scale of Holzknecht, with disks of platino-cyanide of barium"—but his main guide to correct dosage was the reaction produced in the patient's tissues.[38] Coutard developed this subjective evaluation into almost an art. He found that all the patients who were cured by irradiation from 1920 to 1926 had a definite pattern in their radiation response, and he concluded that this pattern was a necessary prerequisite to cure. About 13 to 14 days after the start of treatment, "radioepithelitis of the mucosa" appeared, evolving to denudation and false membrane formation and healing totally by 26 to 28 days into the treatment. At this time, the skin reaction, "radioepithelitis," would begin, healing, in turn, by the 42nd day. If these reactions did not occur in just this pattern, recurrence was bound to happen.[28,38,100] Late effects were often severe; for example, of eight patients treated by Coutard for hypopharyngeal cancer during 1932 and 1933, four were alive and free of recurrence after 5 years. Three had severe skin changes and sclerosis of the treated areas, and one required permanent tracheostomy. All four survivors later died of second cancers appearing in the irradiated area between the sixth and tenth year after treatment.[9]

In 1926, Francois Baclesse joined Coutard, and, in 1936, he became chief of the radiation therapy department at the Radium Institute. He gradually extended the treatment courses to reduce the severe acute and late reactions in normal tissues. He used somewhat higher total doses, but smaller daily doses, which he administered over 60 to 74 days, treating every field every day. He reduced the size of the treatment portals partway through the treatment when possible.[9,39,58,60,92,100]

During the late 1920s and 1930s, many therapists in Europe and the United States adopted the "Coutard technique." Maurice Lenz, of New York City, who trained in Paris, commented in 1934 that "Coutard's method of roentgen therapy of cancer of the upper respiratory tract is being used more widely each year."[101] He noted that the use of machines of higher milliamperage resulted in shorter treatment times, making the method practical for treating large numbers of patients in a clinical setting.[100]

Coutard ended his career in the United States in Colorado Springs. According to Juan A. del Regato, Coutard treated and cured a Colorado mining tycoon named Spencer Penrose who had carcinoma of the larynx in Paris in the early 1930s when del Regato was in training there.* Seven years later, Penrose developed a second primary cancer in his esophagus. Coutard was, by this time, practicing in Chicago, and Penrose went there to be treated again by radiation but did not like the summer weather in Chicago. He bought an up-to-date General Electric 400-kV radiation therapy unit and had it installed in his home, a large estate located behind the Broadmore Hotel in Colorado Springs, so that he could complete his therapy at home in comfort. The treatment this time was unavailing, and Penrose died in 1939 of the esophageal cancer. Penrose had donated his radiation treatment machine to the Sisters of Charity at the Glock-

*Another famous patient treated at the Radium Institute while Dr. del Regato was in training there was the French writer, Francois Mauriac (1885 to 1970). Dr. del Regato relates that Mauriac had had a hemilaryngectomy for larynx cancer in 1932 but had developed a recurrence about a year later. The recurrent tumor was cured by radiation therapy. Mauriac was thus able to continue his career as a distinguished novelist (1952 Nobel laureate) and political and religious writer (del Regato JA, personal communication, 1982). His voice for the rest of his life was "a hoarse whisper."[151]

ner Hospital in Colorado Springs, and when they told him they had no place to put the equipment, he built a new wing on the hospital to house it. After her husband's death, Mrs. Penrose, childless and wealthy, wished to establish a cancer treatment center in Colorado Springs as a memorial to her husband. Coutard, then over 60 years old, was offered every inducement to move to Colorado Springs, and he became Director of Research of the Penrose Tumor Clinic in 1941. He spent the last years of his life in Colorado Springs, where he enjoyed frequent hikes in the Rockies, before returning to France in 1949 at the age of 73. Dr. William Moss, en route to Manchester for a 1-year fellowship in radiation therapy, sailed on the same ship; he relates that Coutard, unfortunately, became quite eccentric in his last years (Moss W, personal communication, 1982). Coutard died in France in 1950.[10,44] Dr. del Regato became head of the brand new Penrose Cancer Hospital in 1949 and was its director for 25 years. He has published a series of historical papers on the pioneers of therapeutic radiology and radiologic physics, including, in 1987, a study of Henri Coutard.[45]

Treatment of Nasopharynx Cancer

Nasopharynx tumors were scarcely ever recognized before the 20th century. In 1901, Jackson found only 13 cases in the world medical literature.[83] Godtfredsen attributed to Michaux the first (1845) report of a histologically verified nasopharyngeal tumor; the patient, a 45-year-old man who had suffered increasing difficulty in swallowing for a year, died immediately after Michaux's attempt to extirpate the tumor.[68]

Martin theorized that the failure to recognize nasopharynx tumors was due to the lack of early symptomatology referable to the nasopharynx and the propensity for early metastatic spread; in many cases, the patient would die of metastatic disease before the primary site was apparent.[117] With the resources of 20th-century medicine, nasopharynx tumors began to be diagnosed more frequently. In 1911, Trotter was able to elucidate the clinical syndrome. He hoped that this might lead to earlier diagnosis and might permit successful surgical treatment. He said that all eight patients on whom he had attempted radical excision had had advanced disease at diagnosis and that all had suffered recurrence by 15 months.[166]

Because the results of surgery were so poor, radiation therapy was attempted early, but the early x-ray tubes could not deliver an adequate dose to the tumor. Applicators were devised to hold radium in the nasopharynx, directly against the tumor, but long-term results were poor. Lymphoepithelioma was described in 1921 as a pharyngeal tumor with distinctive histologic and clinical features.[137,145] It was found to be more sensitive to radiation than the typical squamous cell carcinoma. Although the nature and even the existence of lymphoepithelioma as a pathologic entity were later disputed, most reported series of nasopharyngeal cancers since the 1930s have included separate statistics for lymphoepithelioma and, in general, have shown it to have a better cure rate than squamous cell carcinomas.

As early as 1920, radiation therapy was the treatment of choice for the primary lesion, although there was still some controversy regarding treatment of the neck metastases that were so prominent a feature of this disease. Irradiation of a nasopharynx tumor was (and still is) a test of the expertise of the therapist. Delivering an adequate dose to the tumor in the middle of the head while avoiding overdosage of the normal tissues (skin, brain, eyes, ears, and so on) was a serious technical problem, especially when all that was available were 200-kV x-rays and radium or radon seeds. In addition, therapists only gradually came to understand the patterns of spread of the tumor—especially into the base of skull—well enough to be able to define the tumor volume. Recurrence often resulted from underestimation of the tumor spread rather than from the lack of means to deliver an adequate dose.

The two radiation techniques most often used for nasopharynx tumors during the 1930s and 1940s were the Coutard technique, in which 200-kV x-rays or teleradium was used to deliver a 6- to 8-week course by way of several lateral or anterior fields, and the Radiumhemmet technique, which involved two 2-week courses of external therapy with an intracavitary radium application in between. By the late 1930s, reported cure rates ranged from 0% to about 25% at 5 years. Furstenberg, of Ann Arbor, Michigan, reported 1 of 40 patients alive at 2 years and concluded that "the prognosis remains hopelessly futile."[63] His patients were treated by "radical excision, electrocoagulation, x-ray and radium therapy in various combinations."[63] In 1931, the Radiumhemmet, using their combination of external and intracavitary treatment, had achieved a 5-year survival rate of 11.4% in 70 cases.[68] From the Mayo Clinic, an overall 5-year survival rate of 8.9% was reported, 15.6% (5 of 32) for patients without neck metastases on admission. The patients were treated with intracavitary radium plus external x-ray or teleradium therapy.[124] Lederman wrote, "The results of radiotherapy are universally poor and ours are no exception."[95] Averaging the results of several series from this era, he found a 15% overall cure rate. This was in line with his own results for patients treated from 1933 to 1955 with 200 kV: about 13% survival at 5 years.[95]

A few therapists achieved better results. Lenz wrote that about 25% of patients could be expected to survive for at least 5 years.[99] Using 200-kV x-rays, he reported a 5-year survival rate of 2 of 14 patients with carcinoma and of 6 of 17 with lymphoepithelioma. Martin, of Memorial Hospital, used a combination of intracavitary radium or radon seed plus a 200-kV external beam administered by way of angled anterior fields. He listed the many "gloomy reports" in the literature, but his results were more hopeful: 20 of 80 patients (25%) were free of disease after 5 years or more. If there were no neck node metastases at the time of admission, the 5-year survival rate was 39%. He also analyzed survival by histology: 11 patients of 51 (22%) for carcinoma, 6 out of 14 (43%) for lymphoepithelioma.[117] At M. D. Anderson Hospital, the 5-year absolute survival rate for patients treated with orthovoltage radiation was approximately 30%. To achieve these results with orthovoltage, complex techniques had to be used if severe side effects and complications were to remain within tolerable limits (Fig. 1-12).

The use of supervoltage radiation equipment began in the early 1950s. The supervoltage radiation was important because, with its skin-sparing qualities, therapists could deliver higher doses to larger fields more easily. The technique of irradiation was still the key factor. By the early 1960s, improved cure rates were reported from major centers. In 1963, a series from Massachusetts General Hospital revealed a 48% 5-year survival rate for pa-

Figure 1-12. The orthovoltage technique for carcinoma of the nasopharynx adopted at M. D. Anderson Hospital consisted of eight portals. The nasopharynx was treated through two lateral portals tilted 10 degrees posteriorly and two anterior portals tilted 20 to 30 degrees medially. The four upper and lower neck portals were treated separately with the patient supine and the head rotated away from the side being treated. The superior margin of the lateral portal was about 2 cm above the zygoma. With the differential absorption in bone plus the dose reduction at the periphery of an orthovoltage portal, the dose in the base of skull would be too low to cure many advanced cases. The figure shows the skin reaction at the completion of the radiation therapy course. It was necessary to treat all eight portals each day to avoid moist desquamation. The skin of the lower neck was less tolerant of radiation than the skin of the upper neck, and the upper neck was less tolerant than the fascial skin. It required 8 to 9 weeks to deliver 4500 cGy to the lower neck. Treatment of the primary lesion could sometimes be completed in 7 to 8 weeks, but 9 to 10 weeks was often necessary because of the severe mucositis. The local control rate with orthovoltage was 67% (24 of 36 patients), and the neck control rate was 71%. For comparison, the initial supervoltage results (1954 to 1960) showed a local control rate of 76% (45 of 59 patients) and regional control rate of 81%.

tients treated with supervoltage radiation (2 MeV Van de Graaff). The analysis took into account not just survival rate and histology, but also the stage of the disease and the site of failure. One subgroup of patients, comprising those with involvement of the cranial nerves, the paranasal sinuses, or the base of the skull, was found to have a poor prognosis.[105] Similar results were reported for M. D. Anderson Hospital, where it was found that involvement of the base of the skull or of the cranial nerves resulted in virtually no cures.[61] The treatment technique was modified at M. D. Anderson Hospital in 1962 by increasing the dose to the base of the skull for T3 and T4 lesions; as a result, the local control for the T4 lesions increased from essentially 0% to approximately 50%, and there was an improvement in the overall cure rate. As a result of sophisticated analysis of radiation dosage, treatment volume, and sites of failure, doses were subsequently increased for the T1 and T2 lesions beginning in 1972. The incidence of local control of these less advanced lesions increased from 76% (42 of 55 patients) for patients treated from 1954 to 1971 to 94% (16 of 17 patients) for those treated from 1972 to 1977. Thanks to the meticulous treatment technique, no central nervous system (CNS) complications resulted from the increased dose. Overall, for the 251 nasopharynx cases treated at M.D. Anderson Hospital from the first use of supervoltage radiation in 1954 until 1977, the 5-year survival rate was 52%.[118]

Elective Neck Irradiation

It was gradually recognized that radiation treatment could also be used for neck disease and that it could be used electively for possible subclinical neck disease. Douglas Quick, of Memorial Hospital, was one of the first to advocate elective neck irradiation in the 1920s. Describing the procedure there, he said "Patients presenting with no palpably enlarged metastatic nodes on admission for treatment, are subjected to heavy external irradiation and kept under routine observation."[132,133] In 1928, he reported that of 289 patients with tongue cancer without clinically involved neck nodes at the time of admission, 103 (36%) later developed neck node metastases. This perhaps represented a slight improvement over what would have been expected without any neck treatment at all. Quick used a combination of a 4-g radium pack and x-ray therapy from both sides of the neck.[132,133] In 1933, Bernard Widmann, of Philadelphia General Hospital, reported the results of elective neck

irradiation in patients with carcinoma of the lip. Of 52 patients who had elective neck irradiation, 17% developed neck node metastases; of 72 patients whose necks showed no clinical signs of cancer and were not irradiated, 51% developed neck node metastases. Widmann[179] used "high-voltage roentgen rays" (which in that era meant probably 200 kV) or radium packs.

With the equipment available, it was difficult to deliver an adequate, well-distributed dose to the neck. For example, the crusty surgeon, Stanford Cade, of Westminster Hospital, London, was puzzled, frustrated, and disillusioned by his failure with elective neck irradiation. He had observed some modest success with irradiation of grossly enlarged cervical lymph nodes and properly reasoned that occult disease could be managed by "prophylactic" irradiation. However, his results, as reported in his classic book *Malignant Disease and Its Treatment by Radium*, were disappointing: "In my own series of 100 cases that were [electively] treated, the incidence of metastasis was only slightly smaller than in the group of 50 patients where no treatment was given and the patient kept under observation".[27] This led Cade to recommend ipsilateral radical neck dissection in cancers of the tongue or the floor of the mouth after irradiation of the primary site. Why did Cade have such poor results? For one thing, he was using a teleradium device that could irradiate only a tiny (3.5-cm square) portal. The numbered squares shown in Figure 1-13 were tiny separate treatment fields, almost sure to give an erratic dose pattern. (As Cade[27] noted, "the actual distribution of radiation so provided leaves much to be desired.") But, more importantly, only the midneck was irradiated; the subdigastric and submandibular lymph nodes were completely ignored. In light of these factors, it is little wonder that his elective irradiation was unsuccessful.

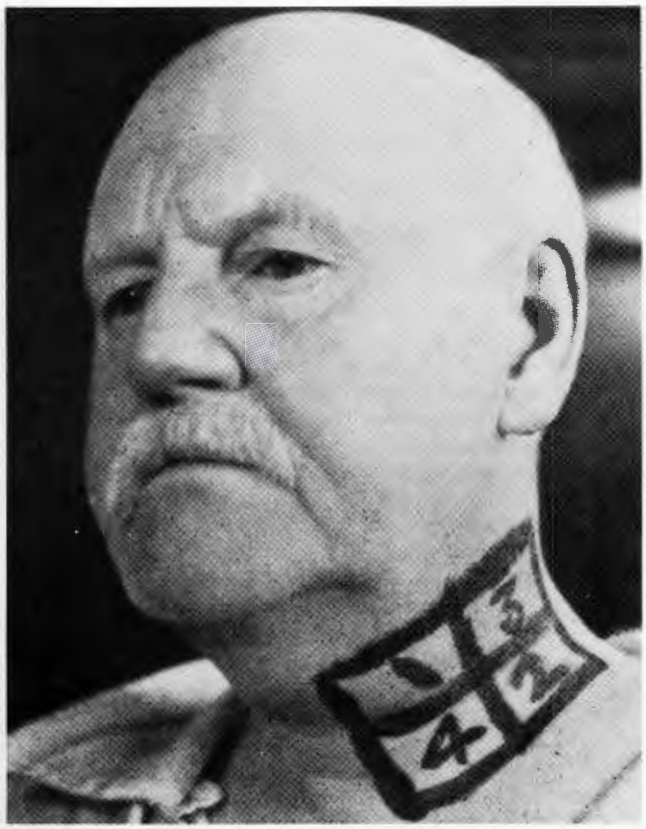

Figure 1-13. Neck treatment portals for Sir Stanford Cade's teleradium technique, which he considered "the best method of external irradiation of the cervical lymphatic field." The teleradium unit at Westminster Hospital, London, could treat a field 3.5 cm in diameter, so four to six ports of entry were required. As Cade described it, "The treatment of the neck . . . requires on an average 60 exposures or 12 hours per port. The dose delivered at a depth of 4 cm from the skin varies from 4000 to 6000 r. The maximum skin dose is 7000 to 9000 r. Moist peeling of the skin occurs at the end of the fourth week. Healing is rapid, and is complete in 2 or 3 weeks." (Cade S. Malignant disease and its treatment by radium. Bristol, John Wright & Sons, 1949:181–182)

Development of Supervoltage Radiation Therapy

Enthusiasm for radiation therapy once again waned in the 1940s as the delayed effects of radiation became apparent. For example, Hayes Martin,[115] an enthusiastic proponent of radiation therapy in the 1930s, wrote the following in a 1948 review article:

> Fractionated radiation therapy for cancer of the larynx brought about some promising initial results. . . . Such early hopes have not been sustained by the experience of the past twenty years. Radiation therapy will cure a small percentage of cases of laryngeal cancer, both extrinsic and intrinsic. This method of treatment, however, is uncertain and fraught with serious complications that may arise at any time, even years following completion of therapy.

Martin turned instead to radical surgery.[109]

It was thought that better results could be obtained if higher doses could be delivered at the proper depth without producing disastrous side effects; this led to the development of megavoltage radiation sources. Low-megavoltage (1 to 2 MeV) Van de Graaff generators came into clinical use in the 1940s, but it was after World War II that supervoltage treatment became practical on a large scale. Cobalt-60 (^{60}Co) could be produced in a nuclear reactor in large enough quantities to make a high-dose-rate, economical teletherapy unit feasible, and the first such units were developed in the United States and Canada in 1951.[146] In a 1958 review, E. Dale Trout reported that about 200 ^{60}Co units were in use throughout the world. By 1973, the number was over 1100.[169]

One of the authors (Million) began his training at M. D. Anderson Hospital on the first ^{60}Co unit in the United States, a ceiling-mounted unit that was developed through a joint effort by the Oak Ridge Institute of Nuclear Studies and the M. D. Anderson Hospital and was manufactured by General Electric.[70] Collimation was accomplished with a set of removable lead cones; the maximum field size was 15 cm × 15 cm. The unit was awkward and required considerable dexterity to accomplish certain techniques.

Accelerators for the production of x-rays were first developed in the 1940s. By 1958, Trout[169] reported that a dozen betatrons were in use for cancer therapy, and several linear accelerators were then in use in England and at Stanford in the United States. Accelerators could also be used to administer electron-beam therapy, and the

first experimental use of this modality began in the 1950s. Betatrons and linear accelerators of increasingly high energy were put in use during the 1960s, and electron-beam treatment units became standard equipment during the 1970s.

Development of the Current Concept of Radiation Oncology

Gilbert Fletcher (and his associate, Fernando Bloedorn) must receive a great deal of the credit for modernizing the radiation treatment of head and neck cancers. Doses were pushed to previously unheard-of levels, and cure rates went up, often accompanied by an increase in complications. Repeated analyses of the specific cause of failure (eg, local recurrence, regional metastases, distant metastases) and complications led to numerous refinements in the techniques of head and neck irradiation.

It is easy to see the development of radiation therapy as a succession of machines, each more powerful than the one before. However, according to Fletcher, the recent developments in radiobiology and treatment planning are even more important than the changing capabilities of the machines used to deliver the radiation.[58] He noted that the prevailing concepts in 1949, when he entered the field, were (1) an "all or none cancerocidal dose," linked with the histology of the disease and not the volume of cancer; (2) a homogeneous dose of irradiation to the entire target volume (both concepts basic to the "Manchester technique" of radiotherapy, developed by Ralston Paterson[129] of the Christie Hospital, Manchester, England); (3) the use of a single treatment modality, either irradiation or surgery; (4) the use of postoperative irradiation only for recurrence, rather than electively; and (5) the acceptance of only radical surgical procedures for use in cancer cases. Fletcher described the changes that have taken place during the years of his career. In addition to the development and wide dissemination of megavoltage equipment, fundamental discoveries in radiation biology were made in the 1950s, such as the discovery that the effect of radiation on cells depends on the presence of molecular oxygen, which was followed by the discovery of areas of hypoxic cells in human tumors.[135,161] In 1956, the survival curve for irradiated cells was found to be exponential.[131] The concept of the steep sigmoid-shaped dose–response curve was developed, demonstrating that small differences in radiation dose could produce wide differences in the result of treatment. The curve was found to be applicable both to tumor control and to damage to normal tissues. Finally, Fletcher describes how, from the 1970s, these new concepts have been applied to radiation therapy. First, there is widespread (if not universal) acceptance of the concept that the volume of cancer is more important than the histology in determining the dose of radiation required for cure (ie, larger tumors, containing higher proportions of hypoxic cells, require higher doses of radiation for control than small tumors). Second, the dose need not be homogeneous through the entire volume treated but can reflect the varying concentrations of tumor that are present. The "shrinking field" technique, originated by Baclesse, is used to deliver lower doses to large areas surrounding a tumor mass for control of "subclinical disease" (disease statistically assumed to be present, but not clinically evident) and to deliver higher doses to a smaller field centered over the bulk of the tumor. Third, irradiation is used as a supplement to surgery in situations in which it is most likely to be successful (eg, the treatment of microscopic or small-volume cancer), just the opposite of the early days when radiation treatment was reserved for the hopelessly large, unresectable tumors. Fourth, as a corollary, large tumors should be resected, if possible. Fifth, because the dose–response curve is steep, an optimum dose, which varies with the clinical situation, has to be determined and maintained. Sixth, conservative surgical resection may be combined with modest doses of radiation to yield a better quality of life for the patient than either modality alone.[58,60]

The fractionation schedules in radiation therapy are still being investigated and revised. The dissociation of acute and late effects on normal tissues as reported by Thames and coworkers supports the current interest in multiple daily fractions.[160]

During the 1960s and 1970s, the specialty of radiation oncology was coming of age. Fletcher estimated that there were 25 full-time radiation therapists in the United States in 1949, compared with more than 1500 in 1980.[58] Many of the early American radiation therapy specialists, such as Fletcher, Maurice Lenz, Traian Leucutia, Isadore Lampe, Franz Buschke, Juan A. del Regato, Fernando Bloedorn, and many others, were foreign born and trained in Europe. However, in the early years, most radiation therapy in this country was administered by general radiologists with only 6 to 12 months of training in radiation therapy. Dermatologists were also briefly trained in the technical aspects of radiation therapy, and they administered superficial therapy for skin conditions. (Some, such as Jesshill Love, went on to become full-time radiation therapists.) Despite the best efforts of the pioneers, radiation therapy was long considered a technical skill (and the therapists as "button pushers") rather than a respectable oncologic specialty. Three-year radiation therapy training programs emerged in the 1960s, but it was not until 1978 that the "general radiology" option (combining diagnostic and therapeutic training) was totally discontinued in the United States in favor of separate training programs.

Sophisticated treatment planning dates from the early 1960s, when computers were first used for external-beam and interstitial isodose distributions. The next phase of treatment planning is just beginning, using computed tomography (CT) to correct for tissue inhomogeneities. CT began with the first experimental two-dimensional reconstruction of inhomogeneities in the 1960s and the prototype EMI brain scanner in England in 1972. Allan M. Cormack[36] and Godfrey N. Hounsfield[79] shared the Nobel Prize for Medicine in 1979 for their contributions to the development of CT. Hounsfield's first experimental machine used a gamma-ray radiation source and required 9 days to scan an object; the computer processing required 2½ hours and produced a paper tape output, which, in turn, required 2 hours of processing to produce an image.[79] The history of CT since then has been one of increasing speed and sophistication in equipment and technique. The first CT machines were used primarily for study of the brain; crude evaluation of the paranasal sinuses and structures of the upper face was also possible. Around 1976, it became possible to study the lower face and neck in detail. High-resolution, thin-section techniques, faster scan times, and the use of iodinated contrast media were developed in the late 1970s, and, by 1985, equipment capable of producing routinely excellent CT images of the entire head and neck

region was available from several competing manufacturers. Developments in the late 1980s included three-dimensional display of CT data and more rapid scan times with 1-second or subsecond scans being the rule. The average CT study will soon take only 10 to 15 minutes (Mancuso AA, personal communication, November 1990). Magnetic resonance imaging (MRI), with its multiplanar and tissue-contrast capabilities, was developed about 5 years after CT. Its full capabilities are only becoming apparent as we enter the 1990s.

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2

NATURAL HISTORY OF SQUAMOUS CELL CARCINOMA

RODNEY R. MILLION

EPIDEMIOLOGY

The estimated number of new head and neck cancer cases (excluding skin cancer) for 1990 in the United States was around 42,800; this represented about 4% of the total new cancer cases for that year.[1] The ratio of occurrence for males versus females was about 3:1 to 4:1. Head and neck cancers are usually diagnosed when the patient is past the age of 40; salivary gland and nasopharyngeal tumors occur in slightly younger age groups. There has been no major change in the incidence of head and neck cancer over the past three decades in either the male or female population, which is a bit surprising, because a common etiologic factor, cigarette smoking, has resulted in a large increase in lung cancer. Cigarette smokers have an increased risk for multiple head and neck primary lesions and also lung and esophageal cancer. Alcohol has also been implicated as a causative factor for certain head and neck cancers, and the effects of alcohol and tobacco seem to be additive.[13] The risk of alcohol consumption without tobacco use is less clear, with some studies showing a slight increase in risk and some studies showing no increase in risk.[10]

Abstinence from smoking eventually reduces the cancer risk. Various studies conclude that 15 years to as long as 30 years is required to approximate the risk of nonsmokers.[2,14]

Multiple cancers of the aerodigestive tract are a result of the tobacco etiology. Panosetti and coworkers found a 9.4% incidence of multiple primary cancers in 9089 patients treated for head and neck cancer between 1975 and 1983 in France.[9] Forty-two percent of multiple cancers were diagnosed simultaneously or within 6 months of the index cancer. Eighteen percent developed more than two cancers. Stage of the first lesion did not predict the risk for a second cancer. Seventeen percent of second cancers were in the esophagus, and 18% were in the lung. In the United States, the risk of a second cancer in the esophagus has been less.

Marijuana smoking has been implicated as a causative agent of squamous cell carcinoma of the upper aerodigestive tract, particularly in young patients (Post JC, Brown T, Cassisi NJ, unpublished study, April 1989).[3,11] Marijuana has been shown to contain carcinogens, produce immunosuppressive effects, and cause mitotic abnormalities in smoke-exposed cell cultures. The risk of marijuana-induced cancer is confounded by simultaneous use of cigarettes.

PREVENTION

Retinoids have been used to try to suppress carcinogenesis. Hong and associates[5] reported the M. D. Anderson Hospital randomized trial of 100 patients comparing placebo and isotretinoin (13-*cis*-retinoic acid) to reduce the risk of a second primary tumor after surgical or radiation treatment of a squamous cell carcinoma of the oral cavity, oropharynx hypopharynx, or larynx. The rate of local, regional, or distant recurrence of the index cancer was unchanged, but the risk of a second cancer was 4% in the isotretinoin group and 24% in the placebo group after a median follow-up of 32 months. Ninety-three percent of second primary tumors were in the head and neck, lung, or esophagus. The side effects and cost of the drug remain deterrents to routine use. Hong and coworkers[4] have reported that isotretinoin suppresses premalignant lesions of the oral cavity.

PRIMARY LESION

Most squamous cell (epidermoid) carcinomas and their variants begin as surface lesions, but occasionally they may arise from ducts of minor salivary glands, in which case they originate below the surface of the mucous membrane. This latter phenomenon is more likely to occur in the floor of the mouth, the base of the tongue, and the nasopharynx. The early surface lesions may show only erythema and a slightly elevated, smooth or mini-

mally roughened mucosa. These are the so-called red lesions, which always deserve consideration for biopsy.

The early asymptomatic red lesions may be either carcinoma in situ or invasive carcinoma. About one third have a component of leukoplakia. Pure white lesions are carcinoma in situ or invasive carcinoma in about 10% of cases. The most common sites for detection of asymptomatic red lesions are the floor of the mouth, the oral tongue, the soft palate, the anterior tonsillar pillar, and the retromolar trigone. Asymptomatic red lesions of the pharyngeal walls, supraglottic larynx, and hypopharynx have occasionally been detected during routine follow-up of head and neck cancer patients.

Each anatomic site has its own peculiar spread patterns, and these are described separately in the following chapters. Muscle invasion is a common feature, and a cancer may spread along muscle or fascial planes for a surprising distance from the palpable or visible lesion. A tumor may attach to periosteum or perichondrium early, but actual bone or cartilage invasion is usually a late event. Bone and cartilage act as a barrier to spread, and these structures are generally spared until the neoplasm has explored easier avenues of growth. Invasion of the edentulous portions of the alveolar ridges occurs earlier because there is no bone present after teeth have been removed. A tumor that encounters cartilage or bone in its path is usually diverted and spreads along a path of less resistance. Slow-growing neoplasms (eg, of the gingiva) may produce a pressure defect or saucerization of the underlying bone with minimal or no bone invasion detected by microscopic examination of the specimen.

Entrance of tumor into the parapharyngeal space allows potential spread from the base of the skull to the root of the neck, but most parapharyngeal space involvement is confined above the hyoid.

Spread inside the lumen of a duct, such as the sublingual, submaxillary, and parotid gland ducts, is not a prevalent pattern. The nasolacrimal duct is frequently invaded in nasal and ethmoid sinus carcinoma.

Perineural spread is an important pathway for tumor spread; no site or histology is immune to this growth pattern. Squamous cell carcinoma and its variants and minor salivary gland tumors, especially adenoid cystic carcinoma, may show this pattern. Local recurrence increases the likelihood of perineural involvement, and tumors may track along a nerve to the base of the skull. Peripheral perineural spread (ie, growth away from the central nervous system) has been seen. Patients with perineural invasion often develop minor neurologic symptoms early in the course of nerve involvement, and only careful questioning elicits these findings. Some nerve palsies are secondary to compression or entrapment rather than to actual nerve invasion. Vascular space invasion is common and increases the rate of lymphatic and distant metastases.

NECK NODES

See Chapter 6 for details of regional lymphatic involvement.

DISTANT SPREAD

The incidence of distant metastases for 5019 cases reviewed by Merino and coworkers[7] was about 11% for squamous cell carcinoma of all head and neck sites. The incidence by primary site and stage is shown in Tables 2-1 and 2-2. The risk of distant metastasis was similar for patients treated by radiation therapy or surgery when compared by stage. As expected, the risk of distant metastasis increases with T stage, N stage, and total stage, but it is most dependent on neck stage. The lung is the most common site of distant metastasis, accounting for 52% of the first recognized sites. Mediastinal metastases are uncommon, representing only 3%. Almost half of the metastases are recognized by 9 months, 80% are recognized by 2 years, and 90% are recognized by 3 years. The

TABLE 2-1. Incidence of Distant Metastasis by Site: Head and Neck Squamous Cell Carcinoma (5019 Cases)*

Primary Site	Incidence of Distant Metastasis (%)
Oral cavity	7.5
Faucial arch	6.7
Oropharynx	15.3
Nasopharynx	28.1
Paranasal sinuses and nasal cavity	9.1
Supraglottic larynx	15.0
Vocal cord	3.1
Hypopharynx	23.6
TOTAL	10.9†

* Minimum 2-year follow-up.

† Excludes 41 patients in whom distant metastasis was found only at autopsy.

(Adapted from Merino OR, Lindberg RD, Fletcher GH. An analysis of distant metastases from squamous cell carcinoma of the upper respiratory and digestive tracts. Cancer 1977;40:147)

TABLE 2-2. Risk of Distant Metastasis by Stage

Stage	Risk (%)
I	2.0
II	5.7
III	8.5
IV	19.5
T STAGE	
T1	5.2
T2	9.6
T3	12.7
T4	16.1
N STAGE	
N0	4.9
N1	11.8
N2	21.8
N3	27.1

(Adapted from Merino OR, Lindberg RD, Fletcher GH. An analysis of distant metastases from squamous cell carcinoma of the upper respiratory and digestive tracts. Cancer 1977;40:148–149)

TABLE 2-3. Risk of Distant Metastasis Related to Initial Control of Neck Disease

Neck Control	Patients	With Distant Metastases (%)
Primary Sites in Oral Cavity; Clinically Negative Neck; No Elective Neck Treatment; Primary Lesion Controlled*		
Neck remained negative	387	3
Neck became positive	94	11
Primary Sites in Oral Tongue, Floor of Mouth, and Faucial Arch; N1, N2A, N2B Neck Disease; Primary Lesion Controlled†		
Neck controlled by initial treatment	134	12
Neck not controlled by initial treatment	46	24
Primary Sites in Oral Cavity and Faucial Arch; N3A, N3B Neck Disease‡		
Primary site and neck controlled by initial treatment	20	5
Primary site or neck not controlled by initial treatment	45	31

* Data from Jesse and associates.[6]
† Data from Northrop and colleagues.[8]
‡ Data from Votava and coworkers.[12]

risk of distant metastasis doubles in patients who develop a recurrence above the clavicles: the risk is 16.7% for those who have a recurrence, even if they are salvaged, and 7.9% for those who never develop a recurrence.

The incidence of distant metastasis is strongly related to initial control, particularly control of neck disease (Table 2-3). Although squamous cell carcinoma can spread from the primary site to a distant site without involvement of the intervening lymphatics, the lymphatic system is probably the common pathway to the venous system. The available data strongly suggest that a significant percentage of distant metastasis occurs as a result of failure to achieve initial neck control. In other words, *untreated occult neck disease may shed tumor into the lymphaticovenous system and produce distant metastases while the lymph node is slowly growing to a size that can be detected.* Although some patients with neck recurrences can be regionally salvaged, many of these patients eventually die as a result of distant metastasis.

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3

EXAMINATION WITH FIBEROPTIC EQUIPMENT

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The fiberoptic telescopes (FOT), both rigid and flexible, are an important addition to outpatient examination and photography (Figs. 3-1 through 3-4). The advantage of the FOT over conventional tools is that it enables the examiner to obtain a better view of the laryngeal surface of the epiglottis, the anterior commissure, the nasal cavity, and the nasopharynx. It also makes it easier to examine a patient with an abnormal epiglottis (eg, a horseshoe or edematous epiglottis) or a large, active tongue.

Indirect mirror laryngoscopy affords a better panorama of the larynx and hypopharynx and should be the preferred method when possible.

Almost every patient can be adequately examined with the rigid FOT. The flexible FOT is useful in situations in which the epiglottis occludes the view of the larynx and in patients with a hyperactive gag reflex that cannot be controlled with a local anesthetic. The field of vision is smaller with the flexible FOT than with the rigid FOT.

The fiberoptic laryngoscope can be inverted to view the nasopharynx, and this technique is preferred over mirror examination. A small-diameter (3-mm) fiberoptic nasoscope may be used to examine the entire nasal cavity and for an anterior examination of the nasopharynx. In a small percentage of patients, especially children, satisfactory examination of the nasopharynx, nose, and larynx may require a general anesthetic.

PHOTOGRAPHY

Photographs of the larynx, pharynx, nasopharynx, and nasal cavity are made on a routine basis in the outpatient clinic (Color Figs. 1 through 9 in this chapter). A 35-mm camera is attached to a rigid fiberoptic laryngoscope equipped with a photographic sheath. Two xenon light sources are coupled together to provide light for photography; this has the advantage over flash-generated light, which must be recycled before subsequent photographs can be made. Fiberoptic cables have been recently replaced with fluid-filled cables, which conduct more light and are more durable. We use Kodak Ektachrome P-800/1600, which is processed at 1600. Several photographs should be made to ensure obtaining a few good ones. An entire roll is often exposed for new lesions because there may not be another opportunity. A local anesthetic is suggested for even the most cooperative patient, because the added bulk and weight of the camera and the shooting process often cause slight jiggling of the scope. Valium (diazepam) is used for the patient with an uncontrollable gag reflex.

Photographs taken with the small-diameter nasoscope are clear and sharp, but difficult to interpret because of the small field of vision. We have no experience with photography with the flexible FOT.

The rigid FOT may be connected to a movie camera or video camera for motion studies.

The scopes are disinfected by soaking in glutaraldehyde (2%) for 20 minutes. Figure 3-5 shows the stainless steel solution holders.

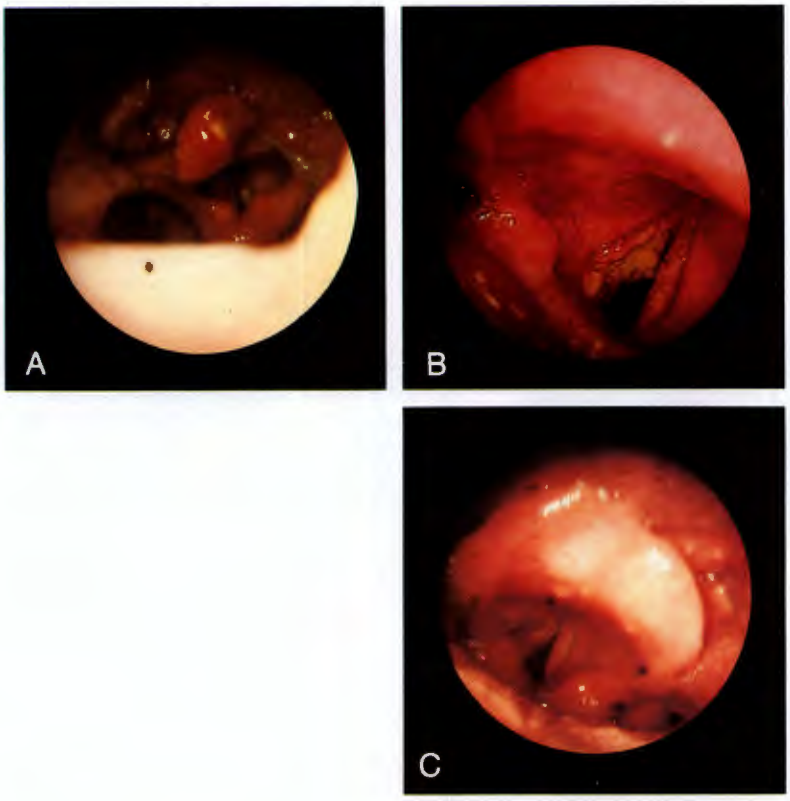
Figure 3-1. Karl Storz rigid fiberoptic laryngoscope with photographic sheath. The distal viewing is warmed in a flame to prevent fogging. The tongue is held as for indirect mirror examination. The scope is rotated to 90 degrees as it is inserted over the tongue to avoid gathering saliva on the distal viewing window. The distal scope often rests against the posterior pharyngeal wall. The posterior pharyngeal wall may be difficult to visualize with a 90-degree telescope.

Figure 3-2. Flexible fiberoptic laryngoscope. A local anesthetic is applied to the oropharynx and larynx. A decongestant spray is used to shrink the mucosa followed by lidocaine to anesthetize the nasal mucosa. A few people may require sedation. The distal viewing window is warmed and inserted under direct vision. If the viewing window becomes covered with secretions, it may be cleared by wiping it gently across the epiglottis.

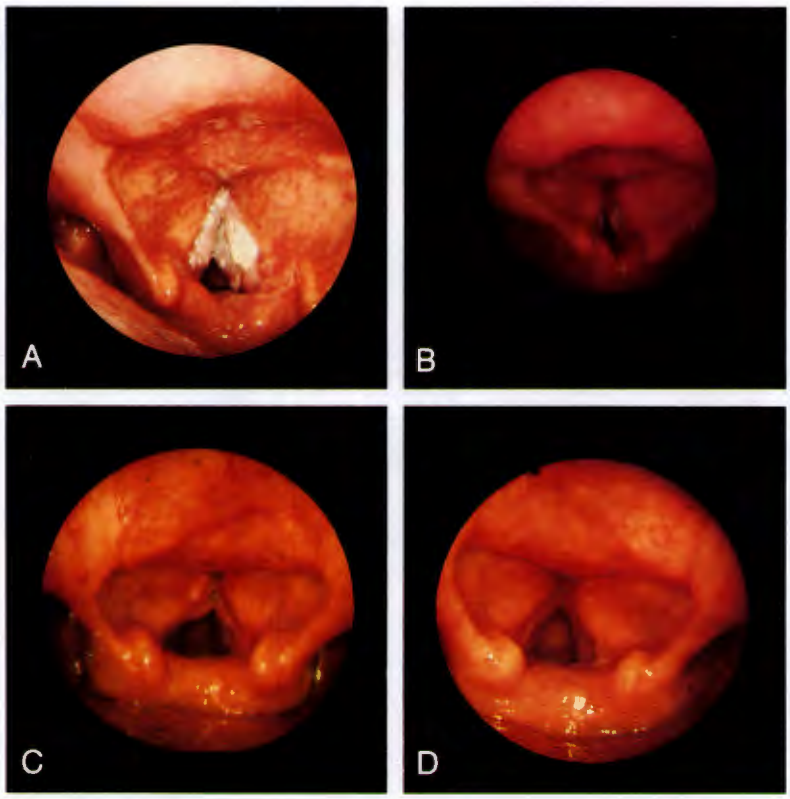
Figure 3-3. A 35-mm camera is connected to a 90-degree fiberoptic laryngoscope with a photographic sheath. Two fluid-filled cables transmit the light from two xenon light sources. An adapter is inserted between the camera and the scope. A trigger handle is added to provide easier operation.

Figure 3-4. Two xenon light sources coupled to the fiberoptic laryngoscope. A video camera may also be attached to the laryngoscope for motion studies.

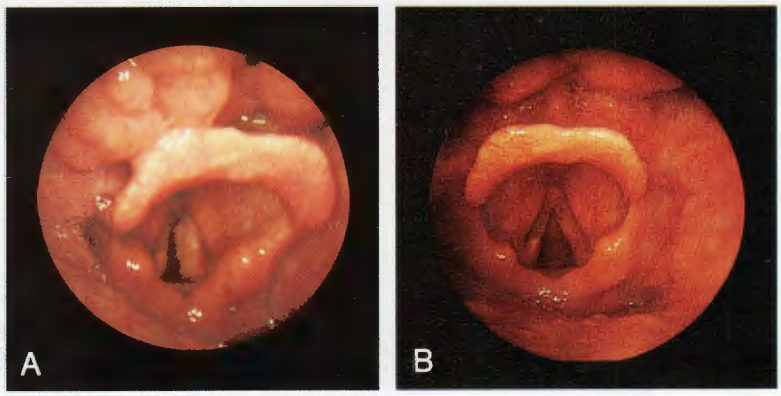
Figure 3-5. Stainless steel solution holders for flexible and rigid scopes.



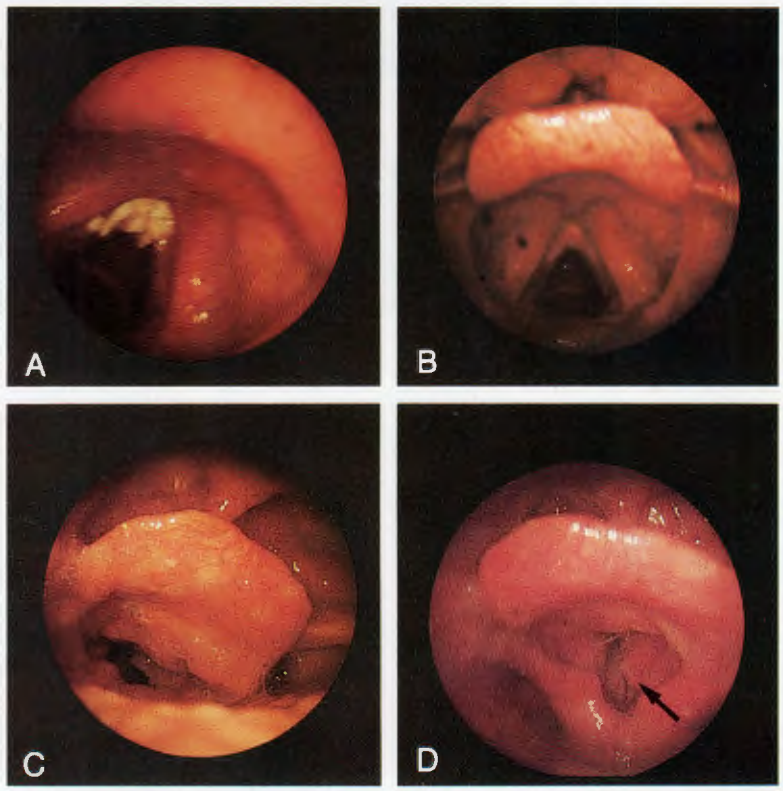
Color Figure 1. (*A*) Early squamous cell carcinoma of the vocal cord in a 60-year-old woman. The larynx was very small, and the tip of the epiglottis rested against the posterior pharyngeal wall and prohibited outpatient examination of the larynx. The right half of the tip was amputated with a biopsy forceps. Photograph was taken 1 year after radiation therapy. Patient was free of disease at 5 years. (*B*) Squamous cell carcinoma of the left vocal cord with subglottic extension and involvement of the posterior left false cord and the face of the arytenoid in a patient with a 3-year history of hoarseness and left-side sore throat. The cord was fixed (T3N0). Treatment was 7440 cGy (120 cGy twice a day) over 6 weeks, cobalt-60. The inferior treatment border was 2.5 cm below the cricoid cartilage. (*C*) Three years after treatment. Mobility has returned to normal.



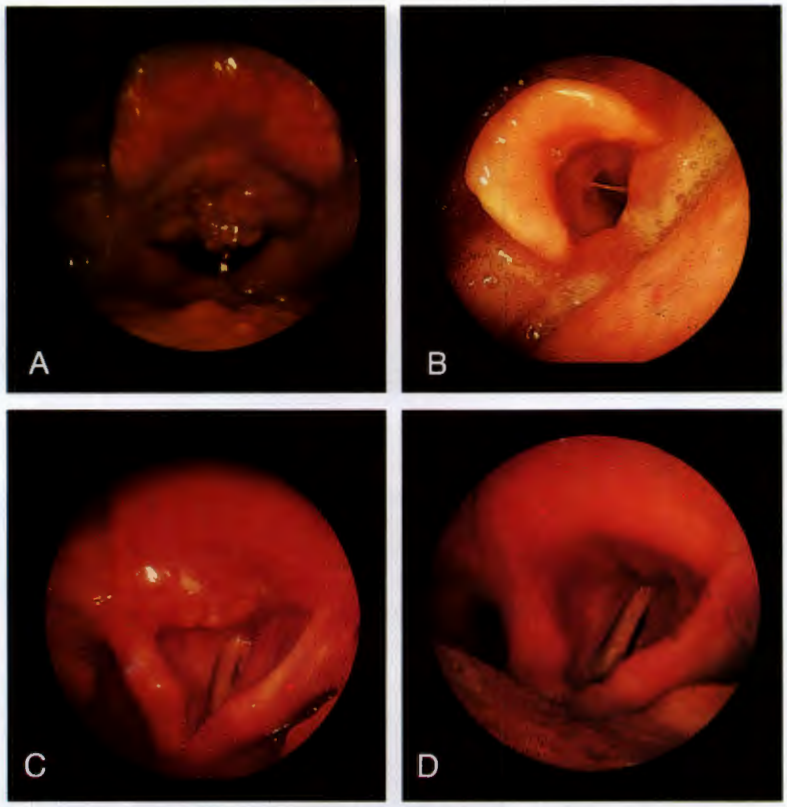
Color Figure 2. (*A*) Squamous cell carcinoma of both vocal cords with subglottic extension, 1 to 1.5 cm, and early involvement of the right false cord. Both cords were mobile (T2N0). Treatment was 6300 cGy in 28 fractions over 5 weeks, cobalt-60. (*B*) No evidence of disease at 3½ years. (*C*) Squamous cell carcinoma of both vocal cords with involvement of the anterior commissure, left anterior false cord, and petiole of the epiglottis. The mobility of the left vocal cord was reduced (T2N0). Treatment was 6750 cGy in 30 fractions over 6 weeks, cobalt-60. (*D*) One month after completion of therapy. Patient was free of disease at 5 years.



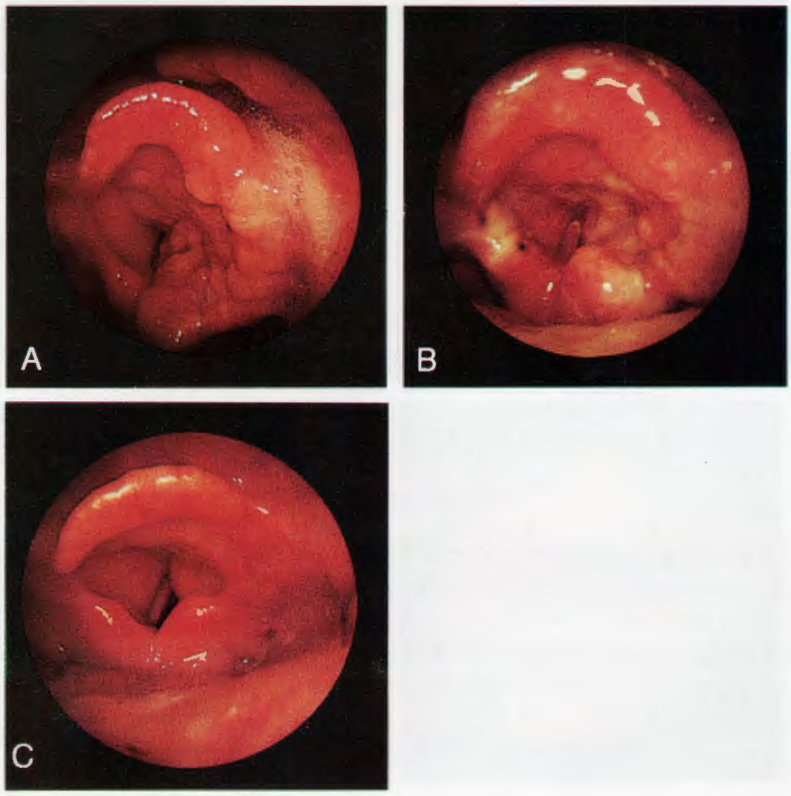
Color Figure 3. (*A*) Squamous cell carcinoma of the right vocal cord (T1N0). There was about 2 mm of normal-appearing right vocal cord anteriorly. Treatment was 6300 cGy in 28 fractions over 5½ weeks, cobalt-60. (*B*) Photograph taken 2 years after treatment. At 5 years, there was no evidence of disease.



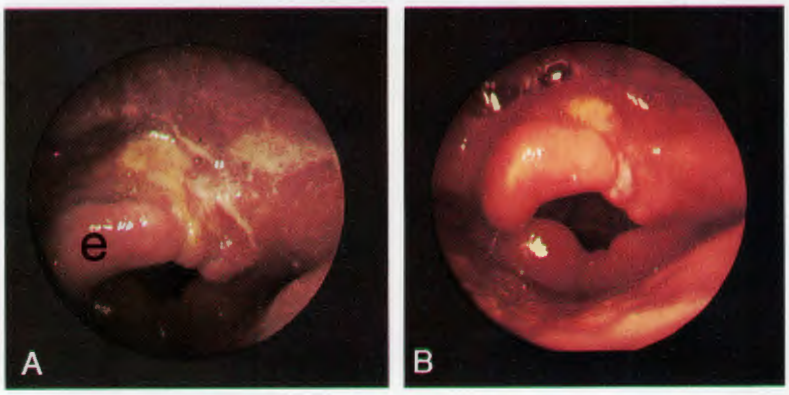
Color Figure 4. (*A*) Squamous cell carcinoma of the vocal cord (T2N0). Horseshoe-shaped lesion involving both vocal cords and the anterior commissure, with a 5-mm subglottic extension anteriorly and minimal involvement of the left false cord. Treatment was 6300 cGy over 5½ weeks (225 cGy per fraction), cobalt-60 (three-field technique). (*B*) Photograph taken 4 months after treatment. There was no evidence of disease at 4 years. (*C*) Direct and indirect laryngoscopy revealed a large lesion of the right infrahyoid epiglottis in a 70-year-old man with a 3-month history of a sore throat and a 1-month history of hoarseness. The larynx was rotated clockwise. There was involvement of the right aryepiglottic fold, the medial wall of the pyriform sinus, and the right posterior false cord (not shown on this photograph). Mobility of the right arytenoid was sluggish. The vocal cords were normal. (*D*) Photograph at 2 months after treatment. The patient was treated with radiation therapy. There was a suspicion of persistence in the right false cord (*arrow*). Biopsies on three occasions were negative. The patient was free of disease at 2½ years; he had moderate supraglottic edema and hoarseness but no pain or airway obstruction. There was considerable fibrosis in the neck and persistent submental edema.



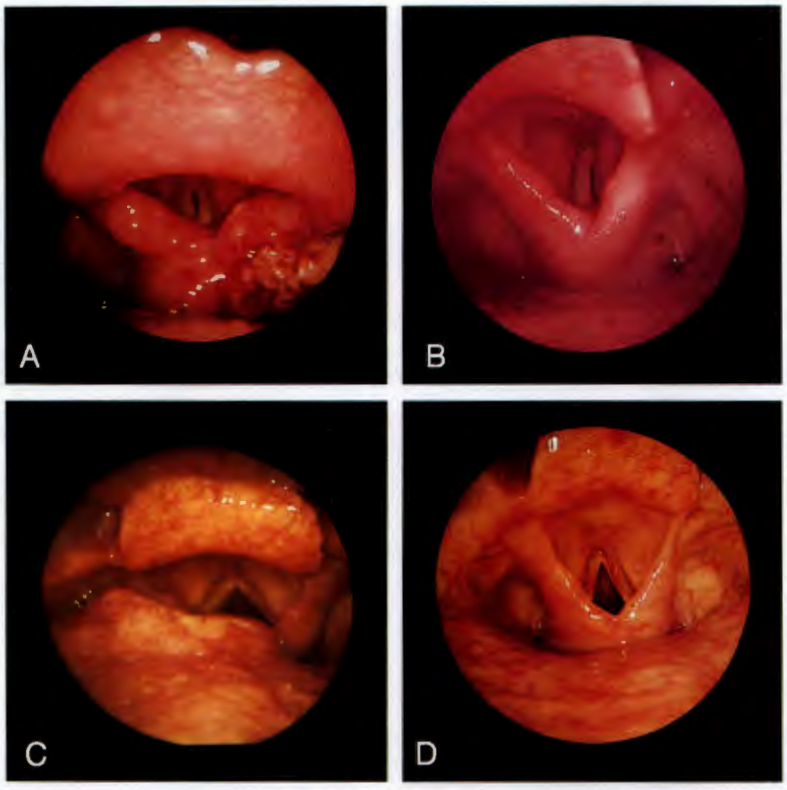
Color Figure 5. (*A*) A 64-year-old man presented with a 6-month history of dysphagia, hoarseness, and a cough that produced mucus, sometimes mixed with blood. Past history included coronary artery disease, hypertension, pulmonary emphysema, and adenocarcinoma of the prostate. He had an exophytic, bulky squamous cell carcinoma of the infrahyoid epiglottis with minimal involvement of the false cords and aryepiglottic folds (T2N0). The anterior commissure and true vocal cords were free of disease. Irradiation was recommended because the patient was medically unsuitable for supraglottic laryngectomy and a borderline risk for total laryngectomy. He received 7000 cGy over 7 weeks, cobalt-60. (*B*) Photograph taken 3 years after treatment. There was no evidence of disease at 5 years. (*C*) A 68-year-old man who was admitted for lens implant was noted to have a mass in the left upper neck. Examination revealed a squamous cell carcinoma of the infrahyoid epiglottis with multiple bilateral neck nodes (T2N3B). The largest lymph node on the left was 5 cm × 3 cm, and the largest lymph node on the right was 3 cm × 2 cm. All of the lymph nodes were mobile. The photograph shows a lesion of the infrahyoid epiglottis with minimal extension to the aryepiglottic fold and pharyngoepiglottic fold. Radiation therapy was elected for treatment of the primary lesion because of the desirability of combining radiation therapy and neck dissection for management of the neck. High-energy x-rays (17 MV) were selected in view of the planned bilateral neck dissection. The radiation treatment plan included 7000 cGy over 7 weeks, 17 MV, to the primary and upper neck. The lower neck received 5000 cGy over 5 weeks, 8 MV x-ray. The posterior upper neck received 1000 cGy, 10 MeV electrons. Staged neck dissection followed at 1 month and 2 months after radiation therapy. (*D*) Photograph taken at 20 months; there was essentially no edema. There was no evidence of disease at 30 months.



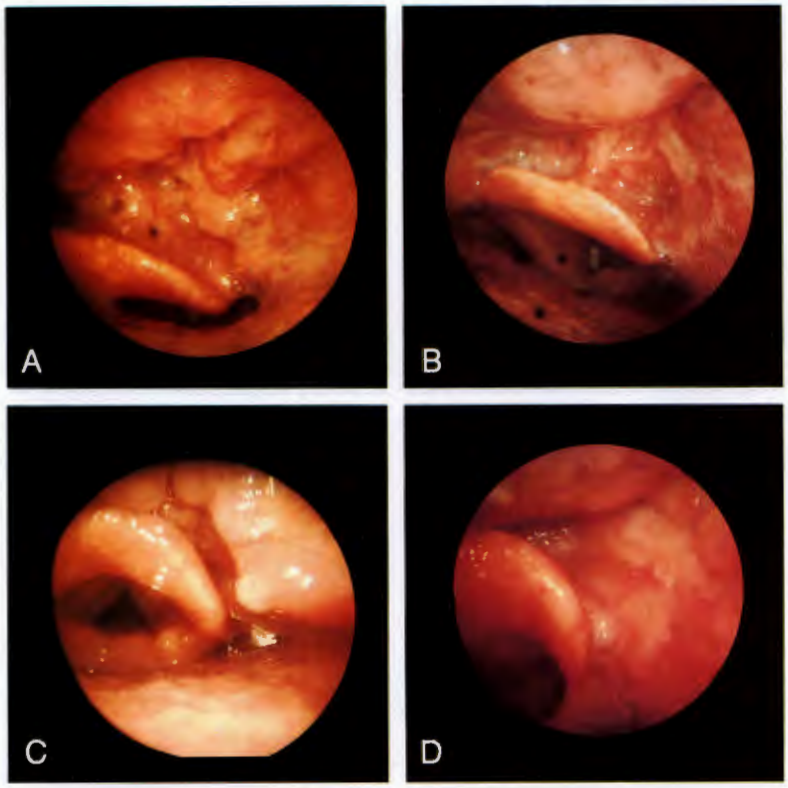
Color Figure 6. (*A*) Squamous cell carcinoma of the right aryepiglottic fold with extension to the false cord, the pharyngoepiglottic fold, and the vallecula and across the midline of the epiglottis (T3N0) in a 52-year-old woman. The surgical alternative was total laryngectomy. The treatment plan was the administration of 4500 cGy and reevaluation. (*B*) There was an estimated 65% regression at 4500 cGy, and it was recommended that full-dose radiation therapy be completed. (*C*) Patient was free of disease at 3½ years.



Color Figure 7. (*A*) Squamous cell carcinoma of the tip of the epiglottis with extension to the right vallecula and pharyngoepiglottic fold. The epiglottis (e) was partially destroyed by tumor (T3N0). (*B*) At 3 months, there was persistent cartilage exposure, but the patient was essentially asymptomatic. There was complete healing at 1 year, and the patient was free of disease at 6 years.



Color Figure 8. (*A*) There was an exophytic lesion on the medial wall of the right pyriform sinus, extending to the aryepiglottic fold and just onto the laryngeal surface of the epiglottis. The left postcricoid area was invaded submucosally. The right vocal cord was immobile, probably owing to invasion of the cricoarytenoid muscle or joint (T3N3B—stage IV). (*B*) The final dose to the pyriform sinus and the lymph nodes was 7400 cGy over 6 weeks (120 cGy twice a day). The enlarged lymph nodes disappeared after 4000 cGy, and it was decided that the neck should be observed. The vocal cord regained full mobility 2 months after treatment. The patient's voice and swallowing were normal at 4 years. (*C*) Squamous cell carcinoma of the posterior pharyngeal wall (T2N0). The treatment plan called for 6000 cGy over 6 weeks, cobalt-60, and gold grain implant, 2000 to 2500 cGy. (*D*) At 3 years, there was no evidence of disease.



Color Figure 9. (*A*) Squamous cell carcinoma of the base of the tongue (T2N3B [N2B–N2B]) in an 82-year-old man. The base of the tongue received 7500 cGy in 40 fractions over 9 weeks (6500 cGy, cobalt-60; 1000 cGy, 8 MV x-ray). There was no neck dissection. (*B*) Photograph taken 22 months after treatment. There was no evidence of disease at 3 years. (*C*) A 71-year-old woman presented with a 4-month history of a lump in the right side of her throat. There was a 4 × 5–cm submucosal lesion in the right base of the tongue, extending to the vallecula. The neck was negative. Biopsy showed low-grade mucoepidermoid carcinoma. The treatment plan was 7500 cGy tumor dose over 8½ weeks, cobalt-60. There was 70% regression at completion of the treatment. (*D*) There was complete disappearance of the tumor at 5 months (patient was free of disease at 30 months).

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4

IMAGING IN PATIENTS WITH HEAD AND NECK CANCER

ANTHONY A. MANCUSO

ROLE OF MODERN IMAGING

Modern imaging methods can provide an extraordinary amount of useful data to those who must diagnose and manage head and neck cancer.[2,4] The potential of magnetic resonance imaging (MRI) and computed tomography (CT) is still unrealized. Most of the information that could lead to optimal use of these powerful imaging tools is available; it must now be dispersed and more fully appreciated. The single most important factor in this educational process is the mutual cooperation between the radiologist and the physicians in charge of patient care. Such a two-way commitment is essential if the costs and small risks of diagnostic imaging are to be justified.

DIAGNOSTIC IMAGING TECHNIQUES

Traditional Radiologic Studies

Plain radiography remains an essential part of the evaluation of the mandible and teeth in cancer patients. Plain radiographic techniques are frequently augmented by orthopantomography and CT; however, the plain films remain a starting point in the overwhelming proportion of patients who have disorders of the teeth and mandible as a result of tumor involvement or in whom the status of dentition is an important factor in treatment planning. Aside from this use and portal planning, plain films have no routine role in cancer diagnosis or treatment planning. Plain films are occasionally done retrospectively as indicated by CT or MRI findings. In the late 1970s and early 1980s, CT techniques were refined to the point where it became apparent that conventional tomographic techniques were relatively obsolete. The most common tomographic technique in practice is orthopantomography for dental purposes. Beyond this, the studies that used to be done by conventional tomographic methods have been virtually completely supplanted by a combination of CT and MRI when these tools are available and economic resources allow their routine use.

Fluoroscopic techniques used in conjunction with barium are most often used for the evaluation of swallowing physiology and screening the mucosa of the esophagus and, to a lesser extent, the hypopharynx for lesions. These studies produce little or no definitive information about the deep extent of lesions, except that implied by the displacement of the pharyngeal wall. If the main aim of the study is to evaluate physiology, some method of recording motion, such as a video tape system or cine radiographic techniques, is necessary. Laryngography and positive contrast tracheography are obsolete in the cancer patient. Tracheography is sometimes used in cases of tracheomalacia or other benign conditions. In the posttreatment patient, studies with a water-soluble contrast medium may be done to identify a leak or fistula.

Sialography is no longer used in patients with parotid or submandibular region masses (see Chap. 27). Dacryocystography may rarely be used to assess the patency of the nasolacrimal system; however, CT and MRI usually provide all the information necessary in patients with tumors close to or involving these structures.

Radionuclide Studies

Radionuclide studies remain integral to the evaluation of thyroid cancer in a selected group of patients. They may be used both diagnostically and therapeutically (see Chap. 31).

Gallium scanning or combined techniques using gallium and bone scanning are extremely useful in evaluating patients with inflammatory conditions involving the sinuses, the skull base, and occasionally the deep soft tissues of the face and neck and sometimes in helping to differentiate inflammation and neoplasm. These studies may be used for both diagnostic purposes and to follow the course of medical therapy. Gallium and bone scans, in particular, have benefited from the new technique known as single photon emission computed tomography (SPECT).

Radionuclide studies remain critical in patients at risk for metastatic disease. The bone scan remains an integral part of this work-up; however, this must be applied selectively and patients triaged for high risk to obtain maximal cost-effectiveness. Liver and spleen scanning may also be used for detecting metastatic disease; however, since patients often have a chest CT as part of the metastatic work-up, it may be more cost-effective to continue the CT examination to include the liver and eliminate the radionuclide study of the liver as part of the metastatic work-up.

SPECT and positron emission tomography (PET) imaging will continue to improve on the information available from radionuclide studies. Tumor imaging may benefit from new agents and tagging of tracers to tumor-specific monoclonal antibodies.

Angiography

The arterial, venous, and lymphatic systems may all be studied by injecting an iodinated contrast agent and recording images with any one of a number of available devices. Lymphangiography has been used in the head and neck region only for investigative purposes (see Chap. 6). The most commonly used angiographic study is arteriography; venography is used infrequently. Angiography may be done with standard rapid filming (cut-film), digital, or cine radiographic recording techniques. When a digital recording device is used, a contrast agent may be injected either intravenously or intraarterially. Intravenously injected studies are generally used for survey studies, whereas arterial injections are used for those studies that require a more detailed and selective study of the various portions of the arterial and venous system in the head and neck region. All of these examinations are relatively safe and of low risk when modern catheter techniques are used. However, because in some situations risks are potentially high, the risks and benefits of all of these procedures should be considered carefully in formal consultation with the radiologist. Alternative safer imaging studies, such as magnetic resonance angiography (MRA), may answer the questions necessary to move forward with management (Fig. 4-1).[1] If angiographic procedures are done, all prior diagnostic studies must be available for review before proceeding with the angiographic examination. A specific plan to obtain the information needed, or therapeutic effect desired, should be agreed on by the referring physician and the radiologist before the study starts. In cases of therapeutic embolization, it is most effective for the clinical and imaging teams to study the patient together and, at times, to do the procedure as a team.

Arteriography

Virtually all arteriography in otolaryngologic disorders is preceded by CT or MRI. It is, therefore, essential to review the diagnostic studies *before* the angiographic procedure. Frequently, all of the information that is required may be obtained by simply repeating an otherwise unsatisfactory imaging study (Fig. 4-2).[1] At the very least, a review of the study usually focuses on the diagnostic issue at hand and, therefore, the examination. This reduces the catheterization time and perhaps avoids needless injection of vessels.

The main purpose for angiography is to characterize, localize, and confirm the diagnosis of a mass lesion seen on other imaging studies. Most commonly, angiography is done to confirm the diagnosis of paraganglioma or juvenile angiofibroma. Rarely, other vascular masses mimic these tumors, but usually atypical imaging or clinical features occur suggestive of some other diagnosis for the hypervascular mass.

MRA is a useful adjunct to standard MRI studies (see Fig. 4-1) and may eliminate some of the current diagnostic angiography done for the lesions just mentioned.

Diagnostic angiography is also done as a prologue to definitive endovascular therapy of head and neck lesions or to endovascular therapy as an adjunct to definitive surgical management of a lesion (see Chaps. 24 and 30). In this regard, the diagnostic portion of the examination should be separated in time from the therapeutic endovascular procedure. This is important for two reasons. First, patients frequently tire if they must cooperate for both diagnostic and therapeutic procedures at one sitting. Patient cooperation is essential in the often protracted period it takes to perform an endovascular therapeutic procedure. Second, the diagnostic study usually needs to be evaluated in detail to plan the safest approach to obtaining the desired therapeutic effect. The patient is best served when the treatment team gathers all of the information available from diagnostic studies and decides on the best management approach before

Figure 4-1. Glomus jugulare paraganglioma in a 35-year-old man. (*A*) Coronal non–contrast-enhanced MRI scan shows the tumor (T) with numerous flow voids representing a large vascular pedicle (*arrow*). The spread to the cerebellopontine angle is obvious; however, this particular sequence does not differentiate tumor from obstructive mastoid disease. (*B*) Contrast-enhanced MRI scan in the same plane as in *A*; tumor, vascular pedicle, and tentorial involvement (*arrow*) are better seen than in *A*. There is still no differentiation between tumor and obstructive mastoid changes. (*C*) Heavily T2-weighted MRI scan differentiates tumor (T) from the brighter, more lateral obstructive and inflammatory mastoid disease better than the images in *A* or *B*; the vascular pedicle (*arrow*) is a little bit more difficult to differentiate from the signal voids caused by bone at the skull base. (*D*) Axial contrast-enhanced MRI scan shows tumor (T) in the jugular vein. Note normal jugular vein (J) on opposite side. (*E*) Sagittal non–contrast-enhanced MRI scan shows tumor (T) growing down the neck within the jugular vein (*arrows*); the localization of tumor within the vein is better appreciated on the axial view seen in *D*. (*F*) Axial MRI scan just below the skull base shows a lesion in the poststyloid parapharyngeal space. From its location, this could be either a paraganglioma or a schwannoma. The numerous, serpiginous flow voids seen within the interstices of the tumor (T), however, are strongly indicative of a hypervascular tumor and in this location almost certainly a glomus vagale paraganglioma. (*G*) Coronal slab MRA viewed anteriorly shows the tumor (T) and partial occlusion of the sigmoid sinus (*arrows*). Compare with the normal sigmoid sinus (S) and jugular bulb (J) on the right side. (Mancuso AA. Diagnostic imaging. In: Meyerhoff WL, Rice DH, eds. Otolaryngology: head and neck surgery. Philadelphia, WB Saunders, 1992:38)

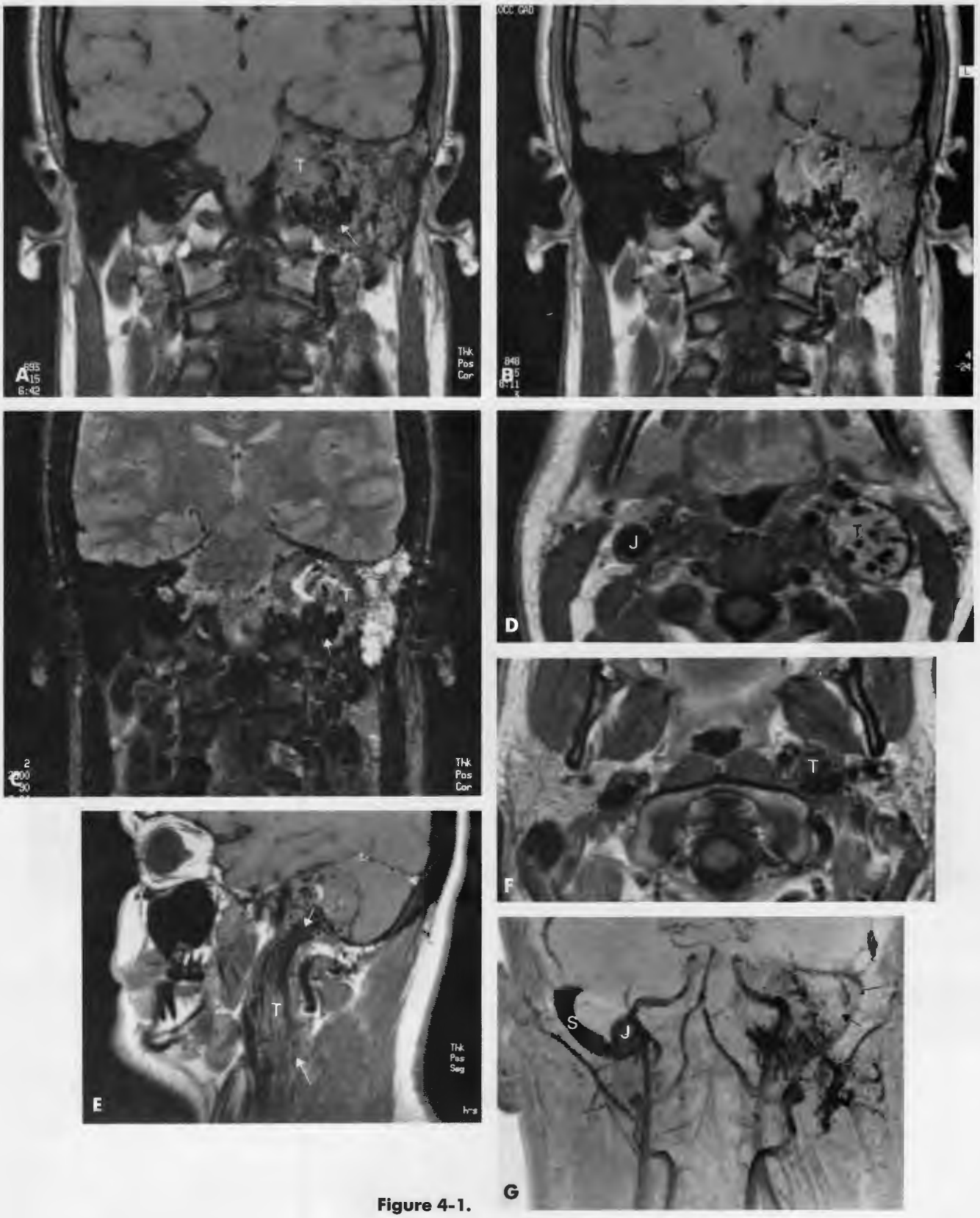


Figure 4-1.

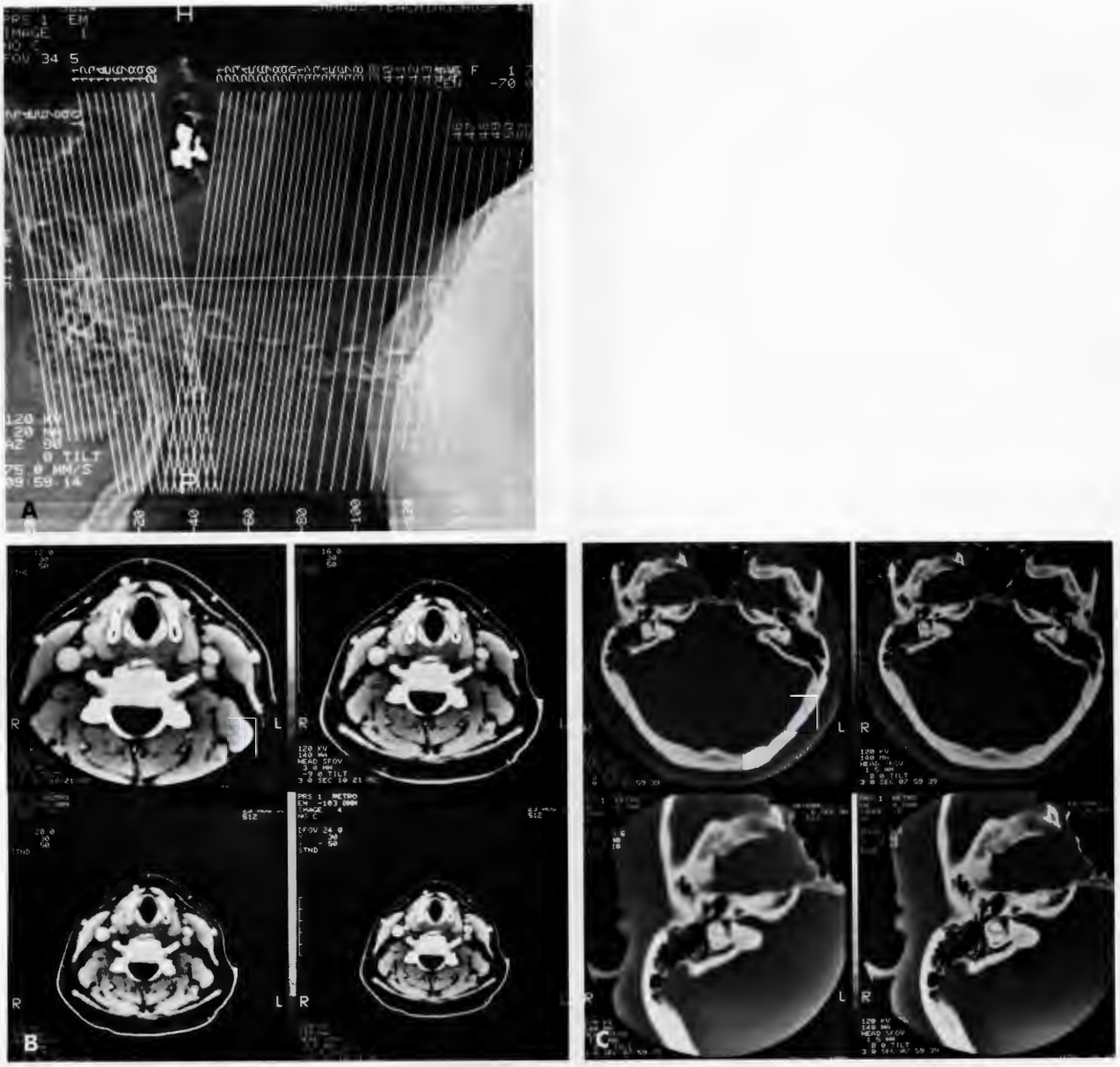


Figure 4-2. The following images represent important considerations in planning and executing a CT study. These are outlined in detail in the text. (*A*) The preliminary digital radiograph is obtained to program gantry angulation, slice thickness, and slice interval. The plane of the section changes in the middle of the oral cavity, both to avoid the fillings that are present and to scan these areas in a logical anatomic plane of interest. In the areas of maximum clinical interest, contiguous 3-mm sections are used; in the lower neck, 3-mm thick sections are used at 5-mm increments. This type of study is typical of that performed for a patient with carcinoma affecting the upper aerodigestive tract, but adjustments are made based on many parameters discussed in this and the following chapters. (*B*) The same section taken in the mid to low neck is reconstructed from raw CT data (not photographically magnified) at increasingly larger fields of view: upper left, 12 cm; upper right, 16 cm; lower left, 20 cm; lower right, 24 cm. The black area around the smaller images represents *wasted* spatial resolution. This series of images also illustrates the optimal opacification of vessels with iodinated contrast material. (*C*) This series of four images illustrates the importance of selecting the correct reconstruction algorithms for a given problem. In the upper left is a bone *window* of a data set processed with soft tissue *algorithm*; the bone detail is not much improved (ie, the bone appears blurred) even by reprocessing the data at a smaller field of view seen in the lower left. The exact same data (ie, the patient was *not* rescanned), in the lower right-hand frame, is processed using bone *algorithm*, which improve edge detection. Note the improvement in quality of bone detail at the lower right compared with the lower left. Improvement in spatial resolution with the choice of a small field of view can also be seen by comparing the lower right-hand picture with the upper right-hand picture. (Mancuso AA. Diagnostic imaging. In: Meyerhoff WL, Rice DH, eds. Otolaryngology: head and neck surgery. Philadelphia, WB Saunders, 1992:54–55)

embarking on either a definitive endovascular or a combined endovascular-surgical approach.

Test balloon occlusion of the internal carotid artery is used in planning surgery for lesions of the skull base or in patients with advanced metastatic disease in the neck with carotid fixation and in whom carotid sacrifice may be necessary. The endovascular interventional radiologist should oversee this procedure. It has become commonplace to integrate this procedure with xenon CT blood-flow studies of the brain. Perhaps in the near future SPECT or PET studies of the brain will be used instead of xenon in identifying patients at risk for significant neurologic deficit if carotid sacrifice is undertaken. Transcranial Doppler studies may also have some role in these situations. Careful coordination between the angiographic techniques and the adjunctive blood-flow studies is essential to ensure patients' safety and useful results.

Venography

Venography is rarely indicated today in patients with the diseases presented in this text. Venography is predominately used to study the dural venous sinuses of the brain and jugular vein. This is probably best done with intraarterial injection into the carotid system and digital recording. CT is a reasonable screening examination for dural venous sinus occlusion, and MRI is potentially better, especially when coupled with MRA capabilities. In fact, MRI and MRA may obviate the need for traditional angiographic study in selected patients (see Fig. 4-1).

Precautions in Angiographic Studies

Precautions are necessary during angiographic studies in patients who have demonstrated hypersensitivity to iodinated contrast media. Untoward reactions are much less common during injections into the arterial system, compared with the venous system. The reason is unknown. Even in the cases of severe allergy to contrast media, risks can be minimized by the use of nonionic contrast agents, premedication, and anesthesia standby. In therapeutic endovascular procedures, one must be very careful to analyze the patient's vascular anatomy to identify potential contraindications to injection of specific vessels. Relative contraindications include uncontrolled hypertension, clotting disorders, and renal insufficiency; all prior imaging studies should be available.

Modern Imaging Techniques

Since the mid-1970s, the practice of radiology has been radically altered by CT, diagnostic ultrasound, and, since 1983, MRI. CT and MRI are by far the most important tools in cancer imaging.

Ultrasound

Too often, ultrasound examinations are done that really have no significant impact on decision making in cancer patients. These examinations add costs, but not information, and should be avoided. Sometimes ultrasound can be the shortest path to a definitive, inexpensive answer, for example, when there is a mass in the upper neck or thoracic inlet that is suggestive of a vascular origin. Here, the duplex ultrasound examination can usually definitively show whether the mass is arising from the vessel, whether it is vascular, or whether it is merely adjacent to and displacing surrounding vessels. This can be very useful in deciding whether to perform a needle biopsy of the lesion or to continue with other diagnostic procedures (for a more complete discussion, see Chaps. 6 and 15). The aim of this example is to sensitize the clinician to the importance of sequencing examinations properly to keep costs at a minimum. Clinicians should be aware that radiologists who are experienced in ultrasound sometimes suggest that it can be a definitive study in a majority of cases; however, in less experienced hands, it really does not provide enough information for patient management and sometimes such claims are just an overstatement of the facts.

Diagnostic ultrasound is particularly valuable in the evaluation of ocular and orbital pathology. Some groups use ultrasound for the evaluation of parotid region masses. It may be used initially to evaluate all neck masses of uncertain etiology; however, the approach at the University of Florida is only to use ultrasound as a primary means of investigation in masses suspected to be vascular or thyroid in origin, and in selected masses at the thoracic inlet. Otherwise, CT is sequenced with fine-needle aspiration biopsy according to the clinical circumstances and preferences of referring clinicians (see Chaps. 6, 15, and 27). Ultrasound is very useful in the evaluation of masses in the thyroid region. The sequencing of ultrasound relative to other functional and anatomic studies is highly dependent on the clinical approach of the referring physician (see Chap. 31).

Ultrasound techniques have recently been combined with the use of newer biopsy guns capable of obtaining core, rather than aspiration, samples of neck masses. Such sampling can be done with a very high success rate and safety in experienced hands. A core sample is especially important when pathologists are more comfortable with histopathology than cytopathology.

Computed Tomography

BASIC TECHNIQUE. The basic technical requirements for head and neck CT imaging include the following:

- Slice thickness: 1 to 2 mm for high-detail work and 3 to 5 mm for routine studies
- Field of view: 9 to 18 cm
- Matrix: 512 × 512
- Scan time: 1 to 3 seconds for routine studies; 4 to 6 seconds for high-detail work
- Capacity for dynamic vascular studies

Injection of iodinated contrast agents is a valuable adjunct when used in conjunction with most intracranial and extracranial CT studies of the head and neck. The risks are minimal, but it is still useful to do a risk–benefit analysis in each patient for the *same* clinical situation. This decision should largely be left to the radiologist. If injection of the contrast medium is considered too dangerous, one might consider doing MRI rather than CT. The contrast agents used with MRI pose a very low risk of serious untoward reaction.

The aims of contrast enhancement in the extracranial head and neck are (1) to determine the vascularity of a lesion, (2) to see the margins of a lesion with greater clarity, (3) to distinguish normal vessels from pathologic tissues (primary tumor and lymph nodes) and study the

effects of pathologic processes on these same vessels, and (4) to aid in differential diagnosis. These goals require that the contrast agent be in the vascular phase throughout image acquisition. In general, this means that on viewing the images the major vessels such as the carotid artery and jugular vein should be obviously different in density than surrounding tissue (see Fig. 4-2). If this is not true, contrast enhancement has not been used effectively in the extracranial head and neck structures. There are several strategies available today that can virtually assure optimal use of contrast enhancement in 90% or more patients.

SPECIAL TECHNIQUES. Dynamic intravascular CT studies are done by injecting contrast medium, usually with a power injector, and scanning the area of interest rapidly. This was previously thought to be potentially useful in the diagnosis of vascular masses and other uses primarily related to neuroradiologic applications. Dynamic scanning serves basically as an option for obtaining images while vessels are maximally opacified. The use of such techniques in differential diagnosis of vascular masses has largely been supplanted by MRI supplemented with MRA when necessary. If there is still a need for additional information, angiography is performed. There are a limited number of CT scanners capable of obtaining images in very rapid sequence. This technology is being applied, but still should be considered developmental; it is not generally available. This can be used for cine studies of the airway and temporomandibular joint.

Advances in computer hardware and software have led to widespread applications of re-formation of CT data in multiple planes. This, in turn, has led to development of three-dimensional reconstruction of the data. One may expect further improvements in the ease of such reconstructions and the user interface with three-dimensional CT data (Fig. 4-3).[1]

CT-guided biopsy is useful in selected patients. It is especially helpful in lesions of the masticator space, infratemporal fossa, parapharyngeal space, and skull base (Fig. 4-4)[4].

ADVANTAGES. The choice between CT and MRI as a primary modality for a given anatomic area or diagnostic problem can be subtle and often controversial. CT is generally more available than MRI. Throughput on CT scanners is generally faster than on MRI, and there are more CT scanners in the field. Also, demand for MRI studies for traditional neuroradiologic and orthopedic problems is high, and backlogs are not uncommon, thus limiting the availability of these units for other studies. Study failures related to claustrophobia are almost nil with CT, whereas a 2% to 5% rate of failure is not uncommon with MRI. In some areas where motion is a potential problem (oropharynx, larynx, and hypopharynx), poor quality or nondiagnostic MRI studies occur in 10% to 20% of cases owing to motion artifact. The failure rate due to motion with CT is 1% or less. Some patients cannot undergo MRI examination because of implanted objects that might unfavorably interact with the strong magnetic and radiofrequency fields of these imaging units. CT is typically 30% to 50% lower in cost than MRI.

Technically, CT is simpler to perform. In general, the examinations are completed within 20 to 30 minutes and can be done on even marginally cooperative patients. Bone detail is much better on CT than MRI, and spatial resolution is still typically better on most CT units.

The morphology of some disease processes appears clearer on CT than MRI; this is especially true of abscesses and inflammatory lesions. In addition, CT shows calcification better than MRI, and this may significantly aid differential diagnosis. Over the past several years, CT has been proved capable of detecting metastases in normal-sized lymph nodes. There are no definitive data to suggest that MRI can match CT's accuracy in staging cervical metastatic disease (see Chap. 6). Nonradiologists prefer CT over MRI because the images are easier to interpret.

The only medical contraindications to the use of CT are related to allergy to the contrast media. This is a relative contraindication that may be overcome in many instances; however, MRI may be reasonably substituted for a contrast-enhanced CT in certain situations and should always be considered a viable option. Few patients are so claustrophobic that they cannot undergo a CT examination without sedation. Sedation short of general anesthesia is effective in virtually all of these patients. CT studies are frequently done on patients who are critically ill or who require general anesthesia. This requires only routine anesthesia equipment, as opposed to the specialized equipment necessary for MRI procedures.

See also the discussion of the advantages of MRI in the following section.

Magnetic Resonance Imaging

Learning to interpret MRI studies involves progressing along a much steeper and longer learning curve than learning to interpret CT studies. Planning and doing an MRI study is also more complex than performing CT.[1]

The intensity of the signal in each MRI voxel is influenced by several variables; these include (1) proton density, (2) longitudinal (T1) and transverse (T2) relaxation times (intrinsic tissue values), and (3) flow (motion). Each of these variables can be influenced by exactly how the operator chooses to design the pulsing sequence that produces the MRI image. This inherent complexity makes MRI more difficult to understand than CT, which depends only on the interaction of the x-ray photon with electrons to create the image.

BASIC TECHNIQUE. An MRI instrument used for studying both intracranial and extracranial manifestations of head and neck disorders should be capable of a certain basic range of techniques. The following are guidelines for performing MRI techniques for abnormalities related to the head and neck:

- Slice thickness: routinely, 4 to 6 mm for two-dimensional Fourier transformation studies (2- to 3-mm thicknesses are desirable in selected circumstances)
- Field of view: 10 to 18 cm for T1-weighted images and 18 to 24 cm for T2-weighted images
- Acquisition matrix: Variable anywhere from 128 × 128 to 256 × 256
- Pixel size: 0.75 × 1 mm to 1 × 1 mm (0.5 mm desirable)
- Acquisition time: No more than 10 to 12 minutes per acquisition, and preferably acquisitions on the order of 2 to 8 minutes
- Paramagnetic contrast available
- MRA, fat suppression techniques, and three-dimensional Fourier transformation techniques available

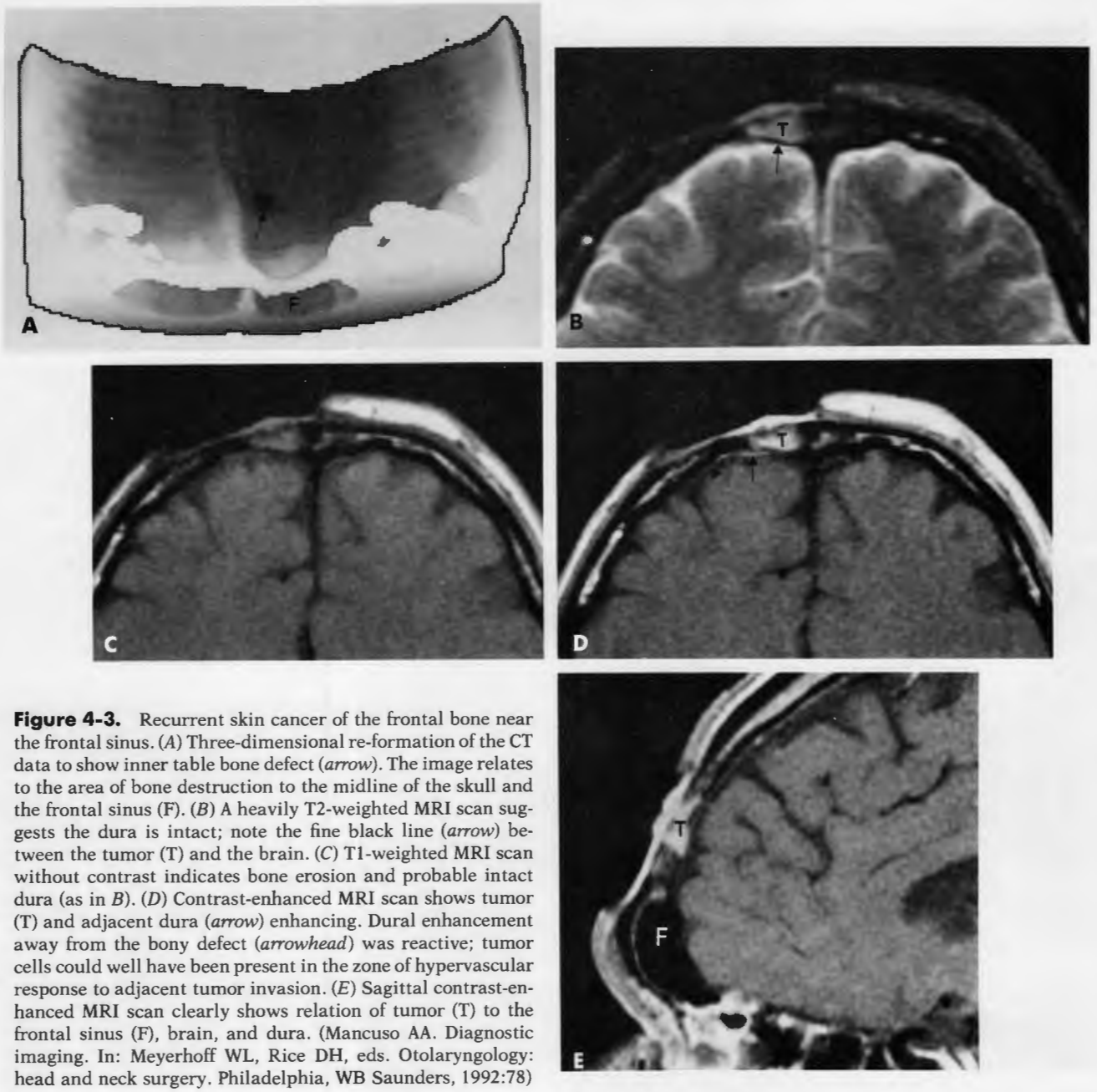


Figure 4-3. Recurrent skin cancer of the frontal bone near the frontal sinus. (*A*) Three-dimensional re-formation of the CT data to show inner table bone defect (*arrow*). The image relates to the area of bone destruction to the midline of the skull and the frontal sinus (F). (*B*) A heavily T2-weighted MRI scan suggests the dura is intact; note the fine black line (*arrow*) between the tumor (T) and the brain. (*C*) T1-weighted MRI scan without contrast indicates bone erosion and probable intact dura (as in *B*). (*D*) Contrast-enhanced MRI scan shows tumor (T) and adjacent dura (*arrow*) enhancing. Dural enhancement away from the bony defect (*arrowhead*) was reactive; tumor cells could well have been present in the zone of hypervascular response to adjacent tumor invasion. (*E*) Sagittal contrast-enhanced MRI scan clearly shows relation of tumor (T) to the frontal sinus (F), brain, and dura. (Mancuso AA. Diagnostic imaging. In: Meyerhoff WL, Rice DH, eds. Otolaryngology: head and neck surgery. Philadelphia, WB Saunders, 1992:78)

- Receiver coils specially designed for head and neck use available

A simple discussion of MRI principles as they apply to head and neck disorders is available.[2]

ADVANTAGES. The choice of whether to use CT or MRI for a particular diagnostic problem is based on many factors. It is sometimes necessary to use both studies, but this should only occur in 10% or less of patients. My opinion is that MRI is best used when focused on a relatively confined area of anatomic interest to answer a specific clinical question.

In general, MRI is the primary examination for any head and neck problem that might involve the brain, leptomeninges, or a process that interfaces between the brain and extracranial head and neck structures (see Fig. 4-3). When examining the extracranial head and neck, the choices are less clear-cut and highly dependent on the clinical situation and, to a lesser extent, the condition of the patient, availability of equipment, and finances.

In choosing between MRI and CT, it is useful to have the basic advantages of each technique in mind. Those for CT were discussed in a previous section. The advantages of MRI include the following:

1. It uses nonionizing radiation. This is especially important in pediatric patients.
2. The intravenous injection of contrast material is often unnecessary and, if used, is probably an order of magnitude or more safer than the iodinated contrast media used in CT studies.
3. MRI can image the body easily in any plane while CT is mainly limited to axial views.

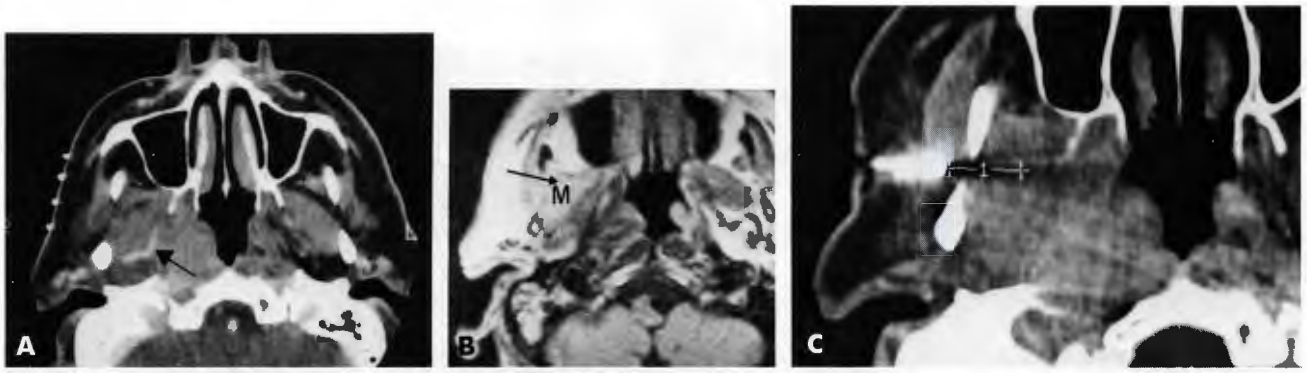


Figure 4-4. This patient had deep facial pain and multiple cranial nerve deficits. Diagnostic MRI study (see *B*) showed an infiltrating mass (M) in the right masticator space and parapharyngeal space. This series of images indicates how CT and MRI may be integrated for a safe, effective imaging-guided needle biopsy in regions difficult to reach by standard biopsy techniques. (*A*) One view from a series of CT scans done with localizing catheters in place on the skin surface. A dynamic study was done with contrast infusion to localize the maxillary artery (*arrow*) and other major vascular structures. (*B*) The localizing CT study was correlated with a similar level from an MRI study showing the target mass (*arrow*), different in signal from surrounding muscle; this aids biopsy site selection and reduces chances of false sampling of muscle. (*C*) Eighteen-gauge ABC needle was positioned so that the cutting action began deep to the facial nerve (note the tip was in the masseter muscle) and distal excursion was directed away from the maxillary artery (see *A*). The depth was also controlled to avoid arterial injury. A core sample was obtained without complications and was hand-carried to the surgical pathology department. The histologic diagnosis was poorly differentiated carcinoma. (Mancuso AA, Harnsberger HR, Dillon WP. Workbook for MRI and CT of the head and neck, 2nd ed. Baltimore, Williams & Wilkins, 1989:9)

4. The contrast between tissue and pathology can be manipulated to a far greater degree with MRI than CT. This can be further aided by the injection of paramagnetic contrast agents.
5. MRI is more sensitive than CT in the detection of intraaxial brain pathology and leptomeningeal processes.
6. MRI is better at determining whether sinuses are obstructed and contain fluid or are invaded by tumors.
7. MRI can better differentiate recurrent tumor from end-stage fibrosis (but not from active scar-granulation tissue).
8. Flow-sensitive imaging techniques can be used to eliminate some angiographic procedures. This is possible on CT, but to a lesser extent.
9. Flow-sensitive and fast imaging techniques can be used to study dynamic processes, such as temporomandibular joint function and cerebrospinal fluid flow.

MRI is contraindicated in patients who have certain implanted devices or objects that might be sensitive to the radiofrequencies used or to the strong magnetic fields. It is possible to scan patients under anesthesia in MRI units, but this task is greatly complicated by the MRI instrument.

IMAGING OF BENIGN AND MALIGNANT NEOPLASMS AND SELECTED AGGRESSIVE INFLAMMATORY LESIONS

The basic contribution of CT and MRI is their ability to find disease spreading beyond the limits of the physical examination of the head and neck, including more advanced endoscopic and physiologic testing procedures. This manifests itself in several ways. Spread beneath intact mucosa is not visible to the endoscopist (Fig. 4-5; see Chap. 15). Deep spread is often palpable but sometimes difficult to assess objectively even with good bimanual palpation combined with inspection and history; however, experienced examiners can often anticipate involvement of the areas that are subsequently proven to be abnormal on CT and MRI (see Fig. 4-5 and Chap. 15). Some regions such as the skull base, pterygopalatine fossa, infratemporal fossa, orbits, and brain are just impossible to reach; here, critical management decisions frequently hinge on imaging findings alone or confirmation by imaging-guided biopsy (see Fig. 4-4). CT and, to a lesser extent, MRI can also provide an objective assessment of all cervical and retropharyngeal nodes. Finally, CT and MRI may be used to follow the course of patients under treatment, to monitor tumor response, and to try to detect recurrent or persistent disease before it becomes symptomatic, when salvage cures are more likely to be successful. Each of these areas will now be considered in more detail.

Basic Tumor Morphology and Spread Patterns: CT and MRI Appearance

On plain CT, most tumors appear to be roughly the same density as muscle. Vague areas of fluid density somewhat less than the "tissue density" of muscle may be visible within the mass. Contrast between fluid and solid elements of the tumor and much lower density fat will be excellent (except for lipomas, which look the same as normal fat). Contrast between tumor and lymphoid tissue (eg, tonsils and adenoids) generally is poor. The tendency for poor contrast between tumor, muscle, and

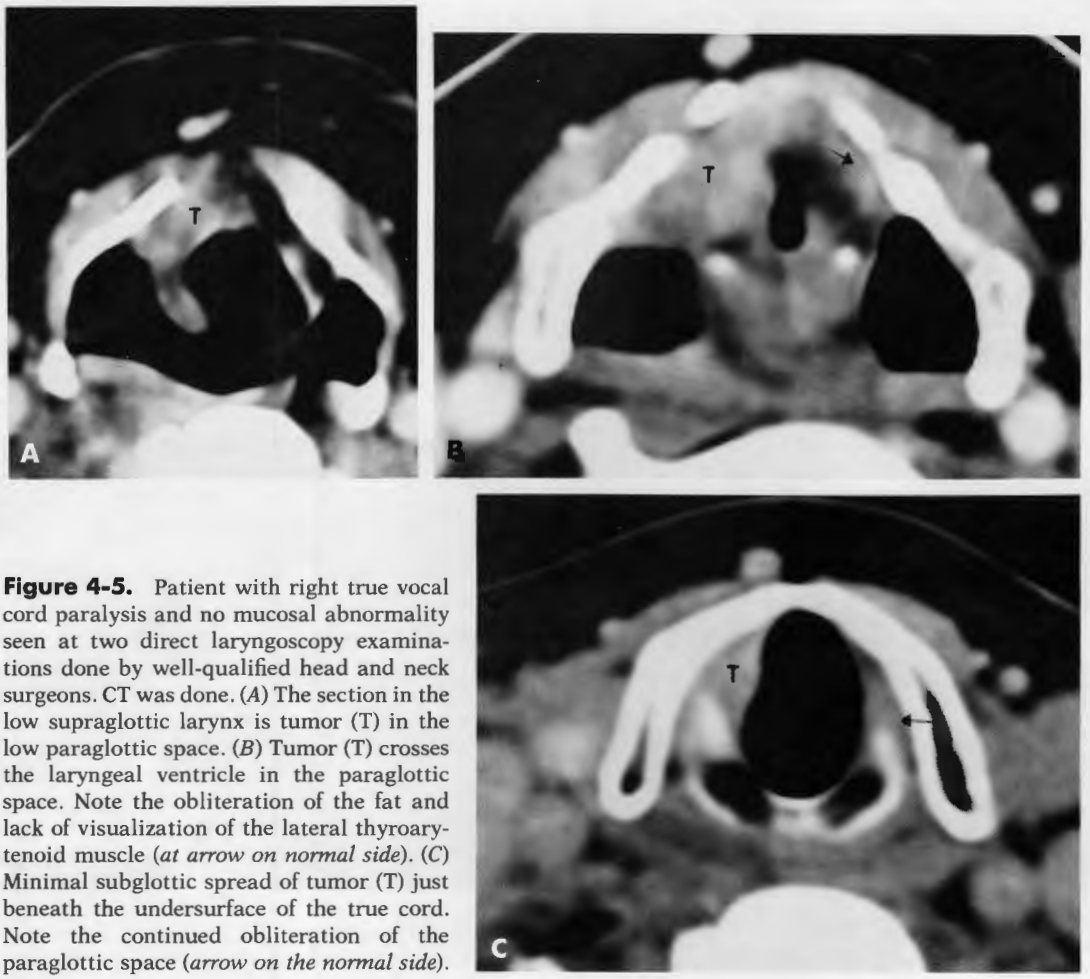


Figure 4-5. Patient with right true vocal cord paralysis and no mucosal abnormality seen at two direct laryngoscopy examinations done by well-qualified head and neck surgeons. CT was done. (*A*) The section in the low supraglottic larynx is tumor (T) in the low paraglottic space. (*B*) Tumor (T) crosses the laryngeal ventricle in the paraglottic space. Note the obliteration of the fat and lack of visualization of the lateral thyroarytenoid muscle (*at arrow on normal side*). (*C*) Minimal subglottic spread of tumor (T) just beneath the undersurface of the true cord. Note the continued obliteration of the paraglottic space (*arrow on the normal side*).

lymphoid tissue severely limits the value of non–contrast-enhanced CT.

Contrast-enhanced CT is another matter. Most tumors accumulate iodine to a greater extent than surrounding muscle; thus, contrast-enhanced CT improves tumor-to-muscle contrast over plain CT (Fig. 4-6). Many tumors invoke an inflammatory response at their interface with normal tissue. This enhancing margin further improves tumor-to-muscle contrast and may help in evaluating the aggressiveness of a lesion, particularly at the tumor–fat interface. Similar improvement in contrast between tumor and lymphoid tissue may occur, but lymphoid tissue, when inflamed, may also enhance, so there is no guarantee of improved tumor–lymphoid tissue contrast with contrast-enhanced CT as compared with non–contrast-enhanced CT. The exception to this is the proven value of contrast-enhanced CT in demonstrating foci of metastatic deposits in normal-sized lymph nodes; in these cases the node enhances, but the metastatic foci do not (see Fig. 4-6 and Chap. 6).

One of MRI's main benefits is that image contrast is based on several intrinsic factors (T1, T2, proton density, flow) as opposed to one (electron density) with CT. Intravenous contrast may also be used with MRI; however, one can control contrast between tumor and normal tissue simply by manipulating the pulse sequences. T1-weighted spin-echo magnetic resonance images generally provide suboptimal contrast between tumor and muscle or lymphoid tissue and excellent contrast between tumor and fat. Standard inversion recovery images offer little more than spin-echo T1-weighted images. Short T1-weighted inversion recovery images usually markedly improve tumor-muscle contrast while maintaining good, albeit different, tumor–fat contrast. T2-weighted spin-echo images provide excellent tumor-to-muscle contrast; however, with increased T2-weighting, the tumor–fat contrast diminishes for many lesions, and signal-to-noise ratio decreases (Fig. 4-7).[1] Exceptions to this are tumors with areas of necrosis or microcystic or macrocystic components. Most nonnecrotic solid neoplasms show signal intensities that roughly parallel that of fat on T2-weighted sequences. Contrast between such tumors and lymphoid tissue is often equally poor on T2-weighted MRI; the most obvious example of this is lymphoma, but this tendency is found with many other tumors. Gadolinium-enhanced MRI behaves in a manner similar to that described for contrast-enhanced CT; tumor–muscle contrast is improved on T1-weighted images, and the margins and internal morphology of the lesion become more apparent (see Figs. 4-1 and 4-7). However, because fat is bright on T1-weighted images, contrast-enhanced MRI diminishes the contrast between tumor and fat; this may cause a significant problem in evaluating tumors in the extracranial head and neck or those invading bones containing fatty marrow (eg, mandible and skull base).

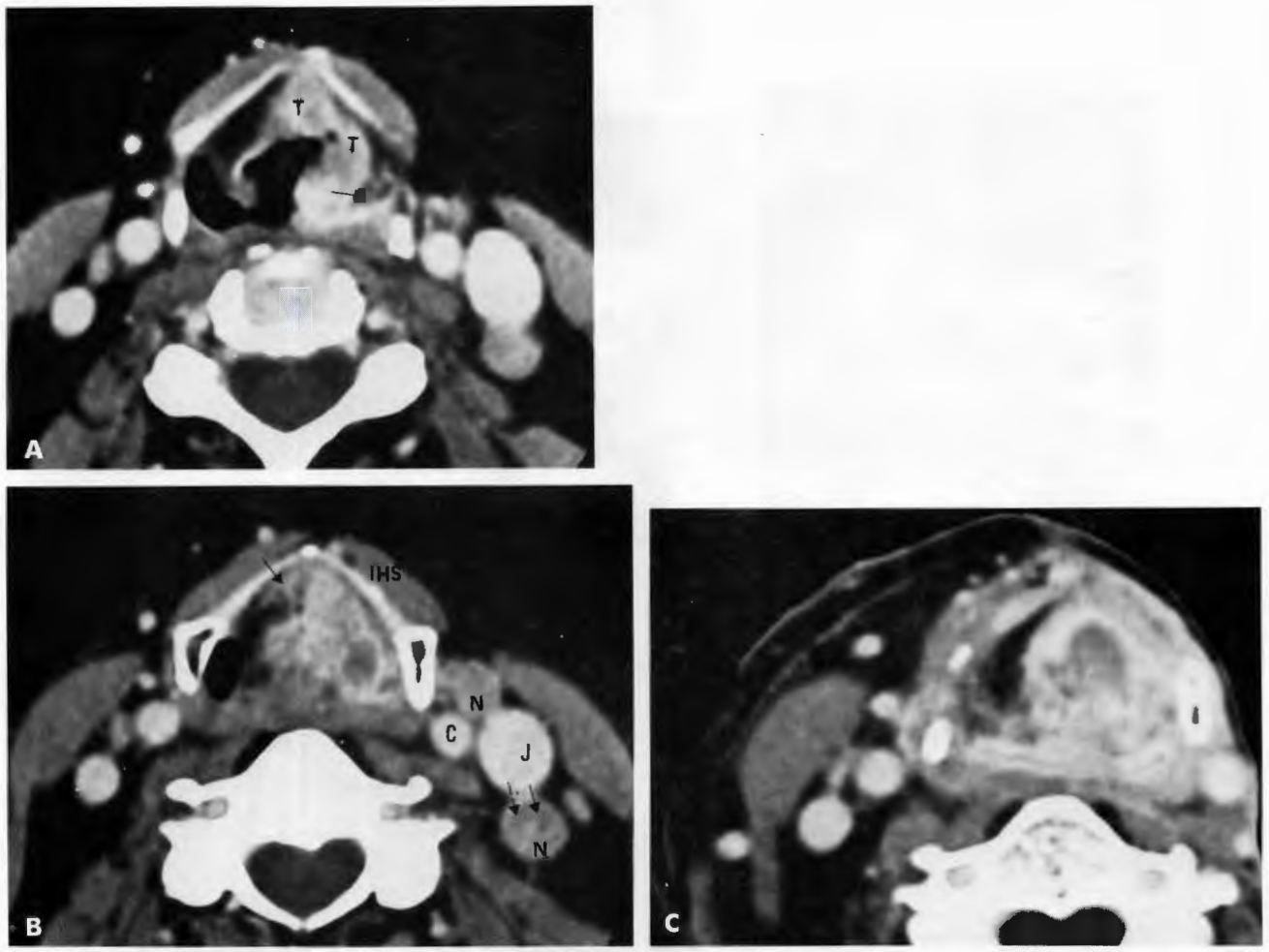


Figure 4-6. Carcinoma of the supraglottic larynx. The neck was clinically N0, and although there was an obvious mucosal lesion present along the infrahyoid epiglottis and epiglottic fold, most of the tumor volume seen on the CT examination that follows was a "submucosal bulge" at clinical examination. (*A*) Section through the mid to low supraglottic larynx shows tumor (T) infiltrating the preepiglottic and paraglottic spaces. There is excellent demarcation of the deep border of the tumor. The fat lateral to the tumor margin is increased in density compared with the more normal fat in the right paraglottic space; this area (*arrow*) most likely represents edema beyond the gross tumor margin. However, this examination cannot exclude the possibility that tumor cells lie within the edematous zone. (*B*) Section taken at the false cord level shows that the tumor is mildly enhanced compared with normal surrounding muscles. Note that the tumor is clearly different in density than the intrinsic laryngeal, thyroarytenoid muscle (*arrow*) and the infrahyoid strap muscles (IHS) lying outside the larynx. Contrast medium also helps differentiate the metastatic nodes (N) from the carotid artery (C) and jugular vein (J). Also note the metastatic foci (*arrows*) in the posterior internal jugular node on the left. (*C*) This scan was done after full-course radiotherapy followed by left radical neck dissection. At the time of the study there was some fullness in the supraglottic larynx but no definite recurrence. CT showed obvious, extensive, submucosal recurrent tumor. Direct laryngoscopy and biopsy confirmed recurrence, and the patient underwent salvage laryngectomy.

Figure 4-7. Nasopharyngeal carcinoma in a 55-year-old man. (*A*) The T1-weighted sagittal image ➤ without contrast enhancement shows tumor (T) to be brighter than the muscle of the posterior pharyngeal wall (*arrow*) and the neck muscles (M). By its signal, however, this could also be normal lymphoid tissue; note that it differs little from the soft tissue of the palate (P), which was uninvolved. (*B*) Contrast-enhanced T1-weighted sagittal MRI scan shows that the tumor (T) enhances, but so would normal lymphoid tissue. Tumor-to-muscle contrast is still good. Tumor is adjacent to the clivus but not definitely invading it. (*C*) Axial, contrast-enhanced MRI scan shows tumor (T) invading the pharyngeal wall. If it were not invasive, the study could not distinguish this from a hypertrophic adenoidal pad. Note the submucosal edema (*arrow*) and mucosal enhancement (*arrowhead*) in the obstructed but not invaded maxillary sinus. (*D*) Spin density (*upper*) and T2-weighted (*lower*) pair of MRI scans shows tumor (T) distinctly different in signal from muscle (M) and mucosal thickening in the maxillary antra (MP). Normal adenoids would be the same signal as tumor on both sequences; in fact, part of the mass in the nasopharynx was normal lymphoid tissue. (*E*) Coronal contrast-enhanced T1-weighted MRI scan suggests clival invasion (*arrow*). (*F*) CT scan done to confirm bone invasion shows cortical thinning (*arrow*) and medullary space sclerosis (*just above arrow*) as evidence of early bone invasion. (Mancuso AA. Diagnostic imaging. In: Meyerhoff WL, Rice DH, eds. Otolaryngology: head and neck surgery. Philadelphia, WB Saunders, 1992:61)

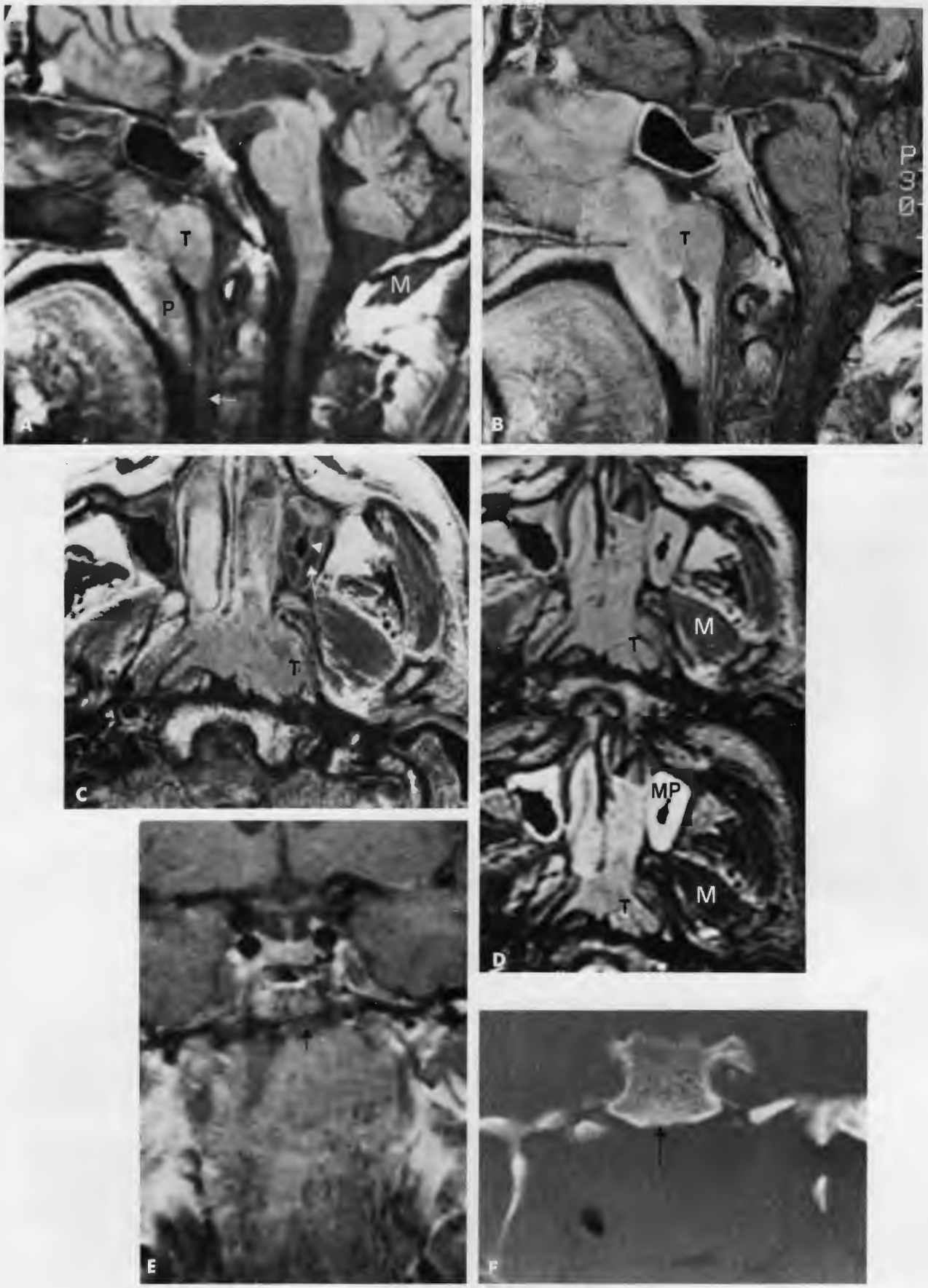


Figure 4-7.

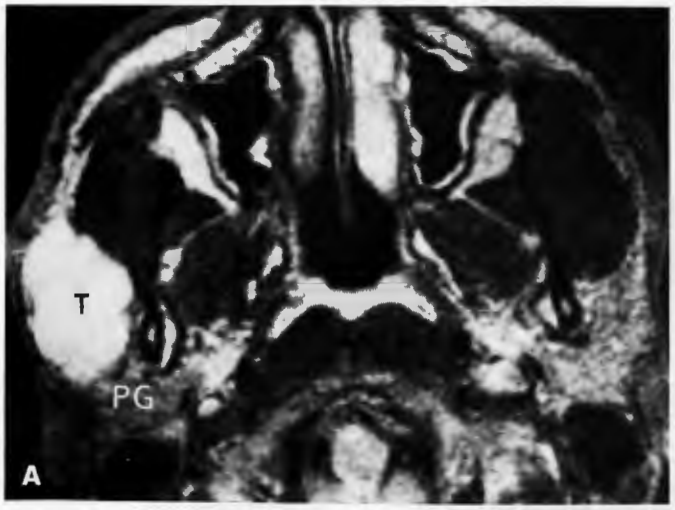
Internal Morphology of Neoplasms

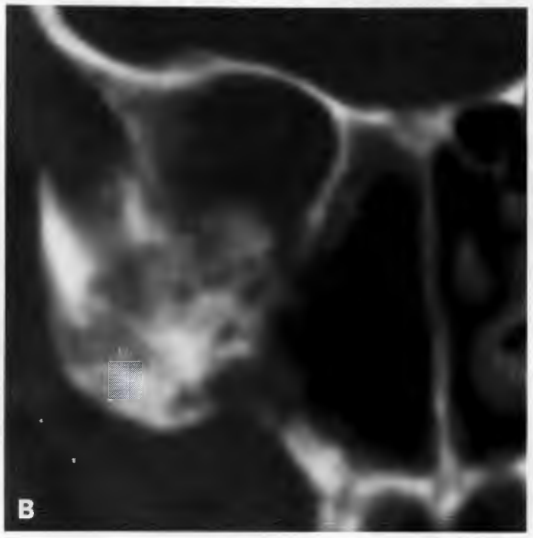
Some specific factors that influence the contrast of particular tumors, to be discussed in subsequent sections, include the following:

- Cellular elements
- Stromal elements
- An acinar or microcystic morphology
- Macrocystic components or necrosis
- Vascularity
- Hemorrhage
- Naturally occurring paramagnetic substances
- Calcification or ossification
- Growth pattern and peritumoral reactive changes
- Prior treatment
- Use of intravenous contrast enhancement

Most tumors grow as a discrete mass. Their general shape is spheroid, but this is modified by surrounding anatomy and growth patterns.

Homogeneously solid tumors on gross appearance may show tremendous differences histologically. Such differences in microscopic structure will affect the MRI appearance of the lesion to a far greater degree than its CT appearance. The differences due to field strengths affect contrast on T1-weighted images. T2 relaxation is relatively independent of field strength. Tumors composed of tightly packed cells and little stroma usually are isodense to muscle on CT and isointense to slightly hyperintense to muscle on T1-weighted spin-echo images. T2-weighted images show the lesion to be roughly isointense to fat, hyperintense to muscle, and slightly hypointense to lymphoid tissue (see Fig. 4-7). More sparsely packed cells or a higher content of cellular water tends to make the lesions appear brighter on T2-weighted images and slightly less intense on T1-weighted images than the standard appearing squamous cell carcinomas. The appearance of CT and T1-weighted images is little affected by stromal elements, although a well-hydrated stroma may cause the lesion to appear somewhat hypointense to muscle on T1-weighted images. Variations in stromal structure can greatly alter the appearance on T2-weighted images. At the extremes of this are the "watery" myxoid matrix and cellular content of mobile water protons seen in chordomas or salivary gland tumors, which causes them to appear bright, and the fibrous matrix of fibroosseous lesions, which makes them appear as dark as muscle or darker on heavily T2-weighted images (Fig. 4-8). One can extrapolate from these extreme examples the varied appearances that result from lesser





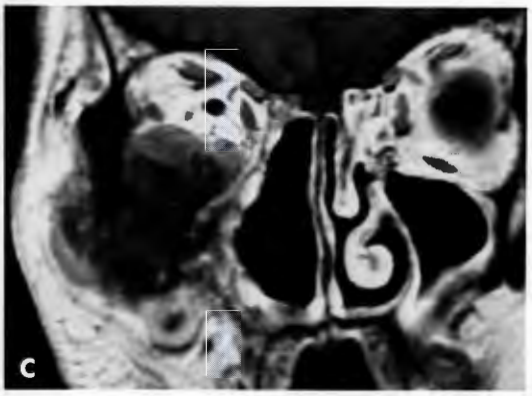


Figure 4-8. (*A*) A heavily T2-weighted image of a benign mixed tumor (T) in the right parotid gland. The tumor is brighter than the parotid gland (PG) and most areas of surrounding fat. This is most likely due to its content of mobile protons. (*B*) CT scan of a patient with osteosarcoma of the maxillary sinus. The osteoid matrix is obvious on this CT section done without contrast infusion. (*C*) A coronal, T1-weighted, contrast-enhanced MRI study shows soft tissue extent of the lesions with great clarity. Note the lack of signal in the calcified portion of the tumor matrix.

amounts of fluid or fibrosis in a reactive matrix, or with the tumor cells themselves.

Tumors may be partially microcystic. Classic examples are lymphangiomas and cavernous hemangiomas. The blood-filled vascular spaces of a paraganglioma or juvenile angiofibroma can have a similar, although less obvious, fluid appearance (see Chap. 30). These tumors may appear slightly hypointense to muscle on T1-weighted MRI. The effect of the increased fluid in the myriad of microscopic spaces is most noticeable as markedly increased signal intensity on heavily T2-weighted images. True neoplasms such as a papillary thyroid carcinoma or benign mixed tumor composed of many acini filled with secretions can have a similar appearance; the actual signal intensity seen depends on relative fluid and protein content of the glandular spaces (see Fig. 4-8).

Both benign and malignant tumors may show focal areas of necrosis and hemorrhage. Some by their nature are macrocystic; however, these are usually benign lesions such as cystic hygromas or teratoid lesions. These varied etiologies mean that the cystic cavities may appear anywhere in a range from smooth, thin-walled, and unilocular to thick, with irregular walls and multiple septations. The density or signal intensity of the fluid area depends mainly on the presence of hemorrhage and protein content of the fluid.

Accumulation of iodinated or paramagnetic contrast material in a lesion grossly reflects its vascularity. The amount of enhancement is also highly dependent on the serum concentration, rate of injection, and rate of wash in and out of the contrast medium relative to the window of data acquisition. Intrinsic (within the tumor matrix) large vessels are occasionally visible on CT and more often seen as flow voids on MRI. Large feeding or draining vessels may also be seen as a sign of hypervascularity on either study. MRA may improve on our ability to recognize truly hypervascular lesions, but standard angiography is essential if MRI or CT is not definitive (see Fig. 4-1). If a blood pool lesion (eg, hemangioma) is suspected, radionuclide blood pool imaging may prove definitive.

A brisk inflammatory response or a primary inflammatory process may mimic a "hypervascular" tumor because of the high density of "leaky" capillaries in these disease processes. Similar peritumoral changes will be discussed in a following section.

Growth Patterns of Benign and Malignant Neoplasms

General Trends

Growth patterns seen on imaging studies are a valuable aid to differential diagnosis. Taken with the history, physical examination, and gross morphology of the lesion, a particular growth pattern can often suggest a specific diagnosis. For example, a highly vascular lesion in the posterior nasal cavity and nasopharynx growing into the pterygopalatine fossa, with regressive remodeling of surrounding bone, in an adolescent boy with nosebleeds is virtually always a juvenile angiofibroma. Lack of extension into the pterygopalatine fossa or an aggressive pattern of bone destruction in the same clinical situation strongly suggests a different diagnosis (see Chap. 24). Growth patterns may also reflect the rate of growth of a lesion. One should resist, however, the temptation to universally link gross morphology and growth patterns to histology. Benign inflammatory lesions may have an aggressive growth pattern, and malignant tumors may have an indolent appearance. This tendency for dysjunction between histology and morphology is predictable in some situations. One specific example is the aggressive appearance of bone destruction seen in the jugular fossa in the jugulotympanic variety of paraganglioma (which is almost always benign) (see Chap. 30). Another is the sometimes smooth contours of an adenoid cystic carcinoma of the parotid gland, even though most larger than 1 cm already have disseminated through perineural spread at presentation (Chap. 27).

Benign Tumors

Benign tumors may be thought of as focal and relatively firm spheres like a handball (see Fig. 4-1) or more diffuse masses with a consistency more like a sponge. All grow along the paths of least resistance. The harder tumors cause relatively more remodeling of surrounding structures to accommodate the increased tumor volume. The softer ones will grow in a more insinuating pattern, like slowly spreading toothpaste oozing into an accommodating adjacent space.

A firm mass in a compartment bordered by bone causes remodeling of the bone. The remodeling is caused by the constant pressure of the tumor on the bone. The demineralization allows the bone to soften and accommodate the mass. If the mass grows slowly enough, the bone remineralizes at its interface with the tumor, but is much thinner than the original bone and in some cases, no bony rim may be visualized. The appearance is that of an expanded space. In fact, there is no real expansion; it is a regressive change made to accommodate a process taking place on a timetable of months to years.

In soft tissue spaces, benign tumors (and less aggressive malignancies) simply push aside adjacent soft tissues such as muscles and neurovascular structures. The vector of such displacements can be very valuable in predicting the type of lesion and site of origin. Perhaps the best examples of this are masses of the parapharyngeal space (see Chaps. 23 and 27).

Most importantly, one must always realize that slow-growing malignancies can show patterns identical to benign tumors. Also, malignancies may arise in preexisting histologically benign neoplasms, and malignancies can cause secondary benign-appearing processes (eg, an obstructing sinonasal cancer can be the cause of a mucocele). Imaging studies must always be carefully scrutinized for findings that may suggest that an otherwise benign-appearing process may be malignant.

Malignant Tumors

PRIMARY TUMOR: LOCAL–REGIONAL SPREAD. Malignant tumors can have a gross morphologic appearance and spread pattern identical to benign tumors and inflammatory lesions.

Mucosal spread is studied by the endoscopist. CT and MRI provide basically no distinction between tumor and inflammatory mucosal changes and the normal lymphoid tissue that lines the upper aerodigestive tract. The superficial lumps, bumps, and attendant variation in airway contour seen on CT and MRI should be used as a

clue for focused observation of adjacent deep structures; this can lead to the detection of significant pathology that might otherwise go unrecognized (see Fig. 4-5 and Chap. 15). One of the best examples of this is the detection of carcinomas originating on the squamous mucosa that lies deep in the crypts of the faucial and lingual tonsils. These lesions may be completely hidden from the endoscopist's view and can grow deeply in the absence of a visible mucosal component.

Once a primary mucosal tumor gains access to the structures and spaces deep to its site of origin, it is free to expand or spread in an infiltrative manner. Obliteration of a tissue plane between a tumor and vessel or muscle does *not* necessarily indicate invasion. Deep fibrofatty tissue planes serve as freely accessible, low-resistance conduits for growth. The disparity of findings can lead to suboptimal disposition in some cases (Fig. 4-9). Infiltrative growth may also follow neurovascular bundles. Like spread along muscle bundles, this pattern of growth can lead to deposition of gross tumor remote from the site of origin (see Fig. 4-9). On CT and MRI such spread is manifested by obliteration of the tissue planes around the neurovascular structures in question. Tumor may be found in the epineurium, perineurium, and endoneurium, and the term *perineural spread* related to imaging studies should be used generically (Fig. 4-10)[1]. Contrast-enhanced MRI may be capable of showing perineural spread better than CT in some cases (see Fig. 4-10).

Spread to bone and cartilage is an extremely important finding in head and neck cancer. Cartilage is relatively resistant to invasion but can be involved. Cancers growing as well-circumscribed lesions may simply erode bone or, if the growth is slow enough, cause regressive remodeling, as described in the previous section on benign tumors. The periosteum is relatively resistant to penetration by tumor. Tumor adjacent to bone tends to slide along the periosteum until it encounters a neurovascular channel or point of muscular attachment to enter. If tumor reaches the bone along a neurovascular or muscle bundle, the access may be easier. The attack at an existing hole forming a neurovascular canal is easy to understand. The point of attachment of muscles is associated with microscopic breaches in the periosteum and bone. These fissures are weak zones in the otherwise resistant periosteum, and it is here that bone and laryngeal framework invasion may begin. CT remains the best study to detect invasion at cortical bone–soft tissue interfaces.

When sclerosis is present, bone invasion cannot be *excluded* and it *may* be present (see Chaps. 16 and 18). Volume averaging coupled with adjacent sclerosis may mimic obliteration of a marrow space by tumor (see Chap. 18).

Obstructed Versus Invaded Sinuses

Edematous mucosa and trapped secretions in obstructed sinus normally contain a very high number of mobile water protons, resulting in high signal intensity on heavily T2-weighted images and making them easy to differentiate from the usually lower signal of tumor obstructing or invading the sinus in question. If the obstruction is chronic, the secretions may lose water and this differentiation may become more difficult; however, most of the time it is simple (see Fig. 4-7).

Posttreatment Reaction and Scarring Versus Recurrent Tumor

The manifestations of posttreatment changes vary greatly with treatment modality, site of pathology, and the original extent and type of tumor treated. Several basic trends are discussed here and then modified appropriately in the subsequent site-specific chapters.

The concept of posttreatment "scarring" must be defined at the outset. The word *scar* usually refers to the end product of the inflammatory response, that is, a zone of relatively dehydrated, hypocellular (collagenous) tissue. On T1- and T2-weighted images this end-stage, dehydrated scar is isointense or hypointense to muscle and shows no enhancement on contrast-enhanced MRI. On CT, it is indistinguishable from muscle or tumor. Unfortunately, many persons also refer to the ongoing inflammatory response (granulation tissue) as scar. This tissue is usually isointense to hypointense to muscle on T1-weighted images and slightly to markedly hyperintense to muscle on T2-weighted images and is enhanced on contrast-enhanced MRI. In other words, it is indistinguishable from tumor. In most areas of the head and neck this subacute inflammatory response resolves and progresses to end-stage fibrosis within 3 to 4 months, or sooner in surgically treated patients. The major exception to this is the dura, which can manifest reactive enhancement on contrast-enhanced MRI for years after surgery in the absence of persistent or recurrent tumor. The deep changes generally parallel the healing process in the skin. Postoperative seromas or hematomas may leave foci of increased signal intensity on T2-weighted images beyond that period. From this discussion two things should be evident: (1) baseline scans intended for use in follow-up should be obtained no sooner than 12 weeks after treatment (surgery, radiation, or both), and (2) T2-weighted along with T1-weighted contrast-enhanced MRI studies probably provide the most information for use in follow-up. The latter is true with the exceptions of detection of recurrent nodal disease and progressive, subtle bone erosion as signs of recurrent tumor.

The response to radiotherapy is similar to that just described in surgery with three important exceptions: (1) during therapy there are significant intratumoral and peritumoral changes; (2) depending on the site irradiated and dose, subclinical edema may persist for many months and evolve to permanent perilymphatic fibrosis; and (3) reactive mucosal changes are common and may persist for months or even years.

During radiation therapy for cancers, the primary site and involved nodes usually show a progressive decrease in size and signal on MRI.[1] At 3000 to 3500 cGy, however, sites of tumor involvement may become frankly edematous and necrotic and peritumoral edema appears. The peritumoral change usually peaks toward the end of therapy. Changes due to necrosis and edema are bright on T2-weighted images. MRI during radiation therapy is, therefore, potentially confusing because the reactive edema and tumor bed may form a conglomerate mass that seems larger than the original tumor. Most successfully treated cancers shrink completely, leaving no obvious mass or a relatively small zone of end-stage

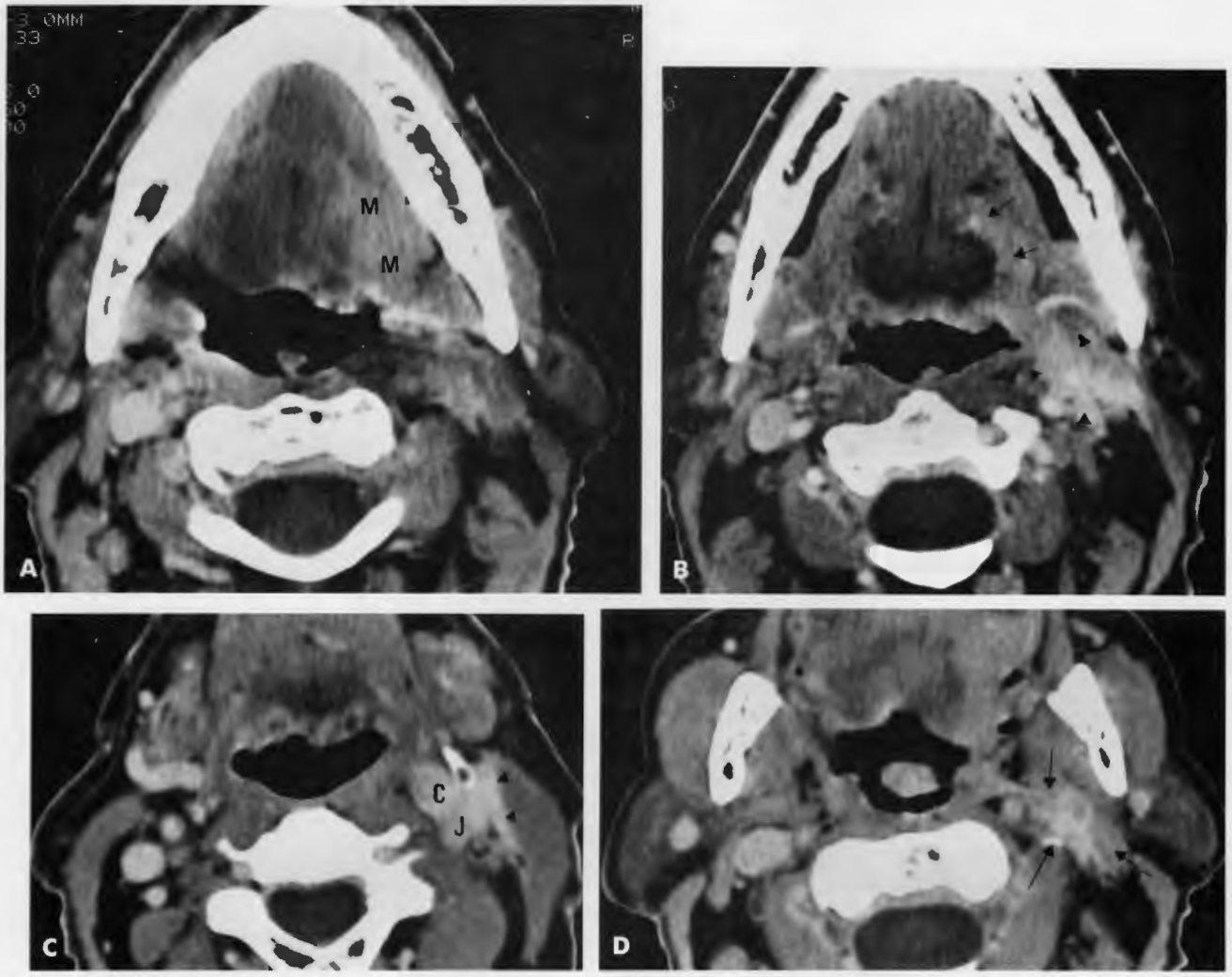


Figure 4-9. CT scan of a carcinoma of the oral tongue. This patient was staged clinically T3N0. Tongue mobility was noted to be somewhat reduced and there was some fullness in the left floor of the mouth, but no palpable extension of tumor into the soft tissues of the neck was present and floor of the mouth extension, if present, was thought to be limited. (*A*) CT at the level of the oral tongue shows a subtle but definite infiltrating mass (M) within the oral tongue extending toward the junction of the posterior third of the tongue and the tongue base. (*B*) Section through the tongue base shows clear evidence of the infiltration of the hyoglossus and styloglossus muscle complex (*arrows*). This should be compared with the normal side. There was also evidence of extension of tumor along these muscles to the area surrounding the styloid musculature and carotid sheath (*arrowheads*). (*C*) A section at the level of the hyoid bone shows obliteration of the tissue planes around the carotid artery (C) and jugular vein (J). Contrast enhancement also extends along the fascia of the sternocleidomastoid muscle (*arrowheads*) compared with the normal side. (*D*) Section taken at the junction of the oropharynx and nasopharynx shows continued obliteration of the tissue planes around the styloid musculature and carotid sheath (*arrows*) compared with normal side. This study showed strong evidence of a very aggressive oral tongue cancer that had extended along the styloglossus and other styloid musculature to grow around the carotid artery and jugular vein directly into the neck and cephalad along the same structures to involve the poststyloid parapharyngeal space. These findings could not be appreciated clinically, or as operated on without preoperative irradiation. All CT findings were confirmed. Gross tumor had tracked along the carotid sheath structures to the skull base and extended along the carotid artery to and below the bifurcation.

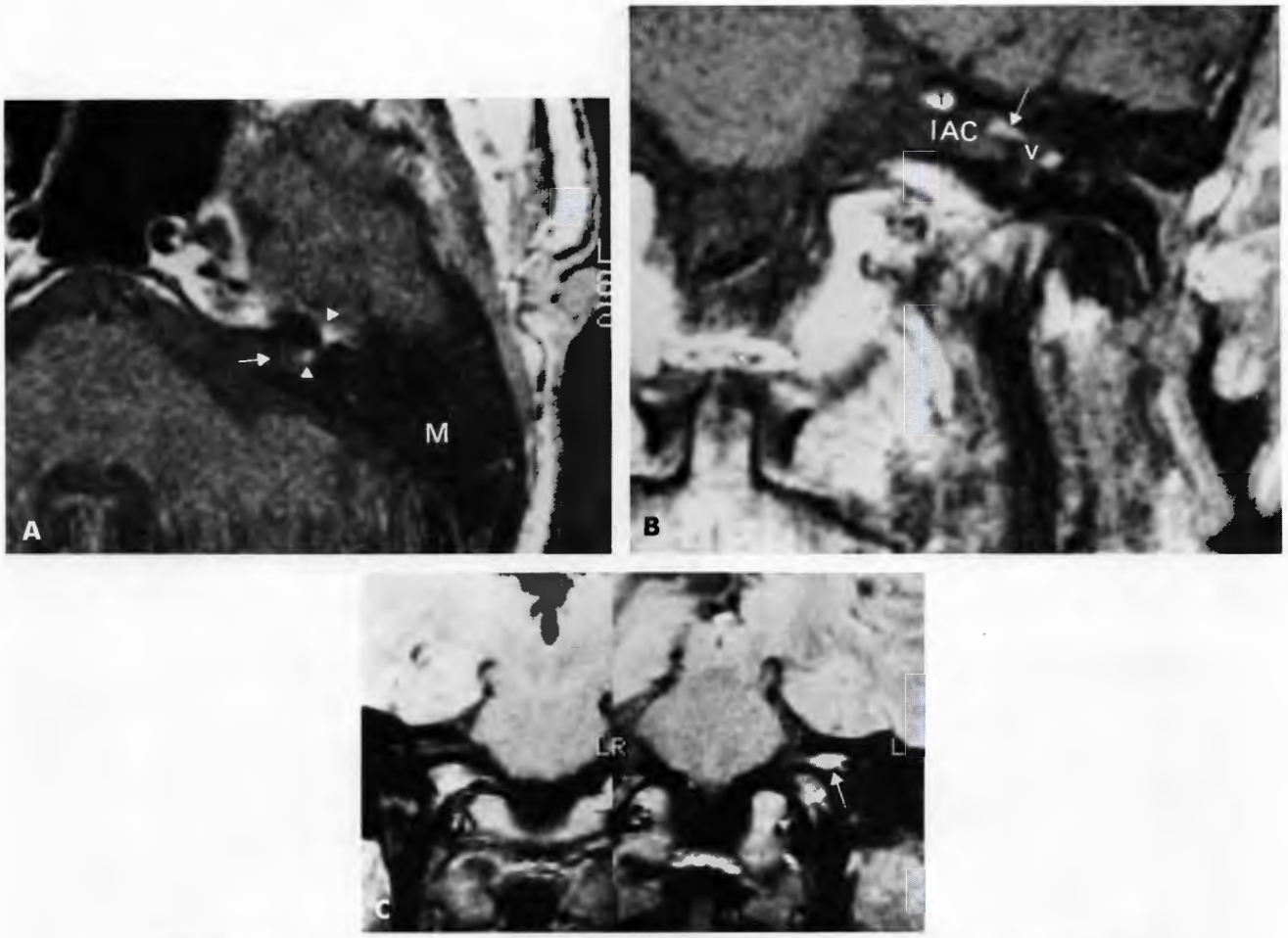


Figure 4-10. Recurrent carcinoma of the pinna and facial nerve paralysis in an elderly man. Two views from the contrast-enhanced MRI study are presented. (*A*) Axial view shows subtle enhancement of the facial nerve at anterior genu, labyrinthine segment, and fundus of the internal auditory canal just adjacent to Bill's bar (*arrowheads*). The arrow indicates the porus acusticus; M, mastoid. (*B*) Coronal section confirms nerve enhancement (*arrow*), not to be confused with normal fat in the petrous apex (f). IAC, internal auditory canal; v, vestibule. Surgery confirmed gross cancer spread in the facial nerve to a point corresponding with the MRI findings; microscopic disease extended to the root entry zone of the facial nerve at the brain stem. (*C*) Inflammatory enhancement of the eighth cranial nerve in the internal auditory canal (*arrow*). This was due to viral neuritis. Enhancement of nerves on contrast-enhanced MRI scan is suggestive of but not absolutely specific for tumor, depending on the clinical circumstances. (Mancuso AA. Diagnostic imaging. In: Meyerhoff WL, Rice DH, eds. Otolaryngology: head and neck surgery. Philadelphia, WB Saunders, 1992:90)

fibrosis by 6 to 12 weeks after therapy. Persistent focal masses that retain a signal intensity greater than that of muscle on T2-weighted images or contrast-enhanced T1-weighted images beyond 3 months should be considered suggestive of persistent disease, and the patients should be observed carefully. Biopsy based on imaging findings alone must be pursued with great caution. This is especially true in the larynx, where deep biopsy can lead to necrosis and loss of a larynx.

Radiation therapy doses over 6500 cGy are often associated with permanent alterations in soft tissues. Thickening of the skin and platysma is common. Strands of tissue density in subcutaneous and deeper fat are probably due to perilymphatic fibrosis and thickening of preexisting fibrous septa in these sites of areolar tissue (see Chaps. 6 and 18). Subclinical, diffuse lymphedema may be present for years in susceptible sites (eg, the supraglottic larynx). There may be profound atrophy and fat replacement of radiosensitive structures such as lacrimal glands, salivary glands, and normal lymph nodes. On the other hand, doses of 4500 to 5000 cGy produce virtually no visible MRI or CT changes within 6 weeks after therapy.

Some benign tumors are irradiated to control their growth (see Chaps. 24 and 30). Typically, 3000 to 5000 cGy is given to such lesions. The tumors may regress completely; however, moderate or minimal shrinkage may occur. Residual masses are usually hypointense to muscle on T1- and T2-weighted images and show no change with contrast-enhanced MRI. Foci of evolving hemorrhage or necrosis, thrombosed vessels, or persistent vascular channels within tumor masses may cause inhomogeneity in their MRI appearance.

The use of imaging studies to monitor the results of

therapy can be an effective adjunct to standard clinical follow-up. A few important limitations of imaging make it wise to follow these general guidelines:

1. Normal imaging cannot exclude the possibility of persistent cancer, and abnormal studies interpreted as residual cancer are sometimes in error.
2. Studies intended to be the baseline for further follow-up should be obtained no sooner than 3 months after surgery or the completion of radiation therapy.
3. The preferred use of CT or MRI as a follow-up study depends on the type of tumor, its site of origin, and whether lymphadenopathy is an important adjunctive consideration in malignant tumors. In benign tumors MRI is almost always preferable.
4. Imaging studies are expensive, and there are no data that suggest imaging is capable of *routinely* detecting recurrence before it is apparent clinically *and* that this leads to improved rates of salvage.

Specific guidelines for use of imaging follow-up are presented, when appropriate, in subsequent chapters. This includes a discussion, in Chapter 6, of the effects of surgery and radiation on lymphatic drainage and the effects these changes have on the pattern and treatment of recurrent disease.

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5

GENERAL PRINCIPLES FOR TREATMENT OF CANCERS OF THE HEAD AND NECK: THE PRIMARY SITE

RODNEY R. MILLION AND NICHOLAS J. CASSISI

Surgery and radiation therapy are the only curative treatments for carcinoma arising in the head and neck. Chemotherapy, used alone, is not curative, and its role as an adjunct to surgery, radiation therapy, or both is being investigated (see Chap. 7).

Most early-stage head and neck squamous cell carcinomas can be cured by an operation or by irradiation, and each modality generally produces similar cure rates for lesions that are similar in size. The selection of treatment rests on such factors as the functional and cosmetic result, the general level of the patient's health, and the preference of the patient and family. Some patients prefer to join in the selection of treatment, but most prefer to be presented with the options and told which is the best treatment for them. The prior experience of a close friend or relative involving an operation or radiation therapy is occasionally a major factor.

ADVANTAGES OF AN OPERATION

The advantages of an operation over radiation therapy, assuming comparable cure rates, *may* include the following:

1. A limited amount of tissue is exposed to treatment.
2. Treatment time is shorter.
3. The risk of immediate and late radiation sequelae is avoided.
4. Irradiation is reserved for a subsequent head and neck primary tumor that may not be as suitable for an operation. For example, a patient might have an early lesion that would usually be treated by radiation therapy, but, because the remainder of the mucosa has premalignant changes suggesting a higher than usual probability of a second tumor, an operation might be selected instead.
5. Pathologic examination of tissues permits identification of patients with more extensive disease than originally determined; for these patients, immediate postoperative irradiation can be added.
6. There is a small risk of radiation-induced malignancy in young patients, particularly those less than 20 years of age. If irradiation is given after the age of 30, the risk is small. The latent period is usually 20 years or longer. This risk must be balanced against the immediate mortality risk of anesthesia, operation, blood transfusion, and so forth (see Chap. 24).

ADVANTAGES OF RADIATION THERAPY

The advantages of irradiation *may* include the following:

1. The threat of a major operation is avoided. An operative mortality rate of only 1% to 2% may seem high to the patient, because there is no immediate threat from radiation therapy.
2. No tissues are removed. Resection of even a relatively small lesion may produce a functional or cosmetic defect. This risk must be weighed against the risk of a radiation necrosis.
3. Elective irradiation of the lymph nodes can be included with little added morbidity, whereas the surgeon must either adopt an attitude of "wait and see" or proceed with elective neck dissection. This is important for lesions with a high rate of spread to the lymph nodes, especially where there is a high opportunity for bilateral spread (eg, the mid-

TABLE 5-1. Multiple Simultaneous Head and Neck Cancers: Control of Individual Primary Sites According to T Stage—Radiation Therapy Group (32 Patients, 67 Primary Sites)*

Stage	Primary Sites	Excluded†	Control After Initial Treatment	Salvage/Attempted	Control After Salvage
T1	25	4	18/21	1/3	19/21
T2	27	4	16/23	1/3	17/23
T3	12	6	1/6	1/2	2/6
T4	3	0	0/3	0	0/3

* Includes three patients who each had three primary lesians treated with radiation therapy alone. Minimum follow-up of 2 years, range of 2 to 20 years.
† Died of intercurrent disease, distant metastasis, neck disease, or recurrence at another primary site within 2 years without evidence of local recurrence.
(McCollough WM, Million RR, Mendenhall WM, Parsons JT, Cassisi NJ. Treatment results for simultaneous primary squamous cell carcinomas of the head and neck. Laryngoscope 1988;98:80)

line floor of the mouth, base of the tongue, soft palate, hypopharynx, supraglottic larynx, and nasopharynx).

4. The surgical salvage of irradiation failures is more likely to succeed than the salvage of a surgical failure. When irradiation is unsuccessful in treating a primary lesion, the cancer almost always recurs in the center of the original lesion. A rescue operation can often be done that would be similar in scope to the initial operation, albeit with a greater risk for a serious complication. In some cases, the rescue operation may entail a much more severe functional or cosmetic loss than if the operation had been performed initially. For example, if an epiglottic lesion suitable for supraglottic laryngectomy is treated by radiation therapy and the treatment fails, the rescue procedure is often a total laryngectomy.

   Rescue of a surgical failure may be attempted by operation, radiation therapy, or both. Surgical recurrences usually develop at the margins of the resection, in or near the suture line. It is difficult to distinguish the normal surgical scar from recurrent disease, and diagnosis of recurrence is often delayed. The response of the tumor to radiation therapy under these circumstances is poor. Surgical failures that present as small mucosal recurrences, however, can often be salvaged by either an operation or radiation therapy or both.
5. The total cost of radiotherapy is often considerably less than for operation (see Chap. 35). Some patients are able to work part time during the treatment course, and retired patients continue some of their activities.
6. Multiple simultaneous primary lesions can be more easily encompassed. It is not unusual for a patient to present for treatment with more than one squamous cell carcinoma occurring simultaneously in the head and neck area, and it usually is advantageous to use radiation therapy as the initial treatment. From 1964 to 1983, 40 patients were identified at the University of Florida as having simultaneous head and neck carcinomas. The soft palate and the floor of the mouth was the most frequent combination. The rates of control of the individual primary tumors with initial therapy are shown according to T stage in Tables 5-1 and 5-2, and Table 5-3 shows control by highest T stage in each patient. Control of disease above the clavicles and survival by American Joint Committee on Can-

TABLE 5-2. Multiple Simultaneous Head and Neck Cancers: Control of Individual Primary Sites According to T Stage—Radiation Therapy Plus Surgery Group (8 Patients, 19 Primary Sites)*

			Control After Initial Treatment		
Stage	Primary Sites	Excluded†	Radiotion Therapy Alone	Surgery ± Radiation Therapy	Control After Salvage
T1	7	5	1/1	1/1	2/2
T2	9	5	1/2	2/2	4/4
T3	2	1	1/1	0	1/1
T4	1	1	0	0	0

* Minimum follow-up of 2 years; range of 2 to 20 years. Three patients with triple primaries.
† Died of intercurrent disease, distant metastasis, neck disease, or recurrence at another primary site within 2 years with no evidence of local recurrence.
(McCollough WM, Million RR, Mendenhall WM, Parsons JT, Cassisi NJ. Treatment results for simultaneous primary squamous cell carcinomas of the head and neck. Laryngoscope 1988;98:80)

TABLE 5-3. Multiple Simultaneous Head and Neck Cancers: Control With Initial Treatment According to Highest T Stage (40 Patients)*

Highest T Stage	Patients	Radiation Therapy Alone (32 Patients)			Radiation Therapy Plus Surgery (8 Patients)		
		Excluded†	Control of One Site Only	Control of All Sites	Excluded†	Control of One Site Only	Control of All Sites
T1	5	0	1/5	4/5	0	0	0
T2	20	0	5/15	9/15	3	1/2	1/2
T3	11	3	3/6	1/6	1	0/1	1/1
T4	4	0	0/3	0/3	1	0	0

* Minimum follow-up of 2 years; range of 2 to 20 years.

† Died of intercurrent disease, distant metastasis, or neck disease within 2 years.

(McCollough WM, Million RR, Mendenhall WM, Parsons JT, Cassisi NJ. Treatment results for simultaneous primary squamous cell carcinomas of the head and neck. Laryngoscope 1988;98:81)

cer (AJCC) stage are shown in Table 5-4. Radiation therapy alone was administered initially for the primary lesions in 32 patients, with immediate neck dissection added in 11 patients. Eight patients had a combination of irradiation and surgery for the primary lesions. The local–regional control rates were good for stages I and II. However, when one of the lesions was a T3 or T4, the cure rate was poor.[18]

It is incumbent on the consulting physician to look carefully at all mucosal areas because of the possibility of a second lesion and the obvious change in treatment planning. An odd distribution of lymph node metastases is often a clue to a second primary lesion.

RISK OF SECOND MALIGNANCIES AS A FACTOR IN TREATMENT DECISIONS

Adult patients with squamous cell carcinoma of the head and neck treated by high-dose radiation therapy alone have no greater chance of a second head and neck cancer than those treated by an operation.

The risk for developing a second primary cancer for 1163 patients with squamous cell carcinoma who were clinically free of disease for at least 5 years after initial treatment is outlined in Table 5-5. The follow-up period was 8 to 25 years. There is essentially no difference in the risk of a second cancer either in the initial site, in a marginal site, or in remote head and neck sites for the categories of surgery alone, radiation therapy alone, and combined treatment. The soft palate group had the highest incidence (33%) of new head and neck squamous cell carcinomas 5 years after successful treatment.[12]

Parker and Enstrom[24] compared the risk of a second primary head and neck cancer for 2151 patients treated by surgery or irradiation and observed for 5 to 30 years at the University of California Los Angeles. There was no difference in the frequency or interval to second cancer when comparing surgery, radiation therapy, or surgery combined with radiation therapy.

Harper and coworkers[7] calculated the 5- and 10-year risks in irradiated patients for a metachronous head and neck carcinoma in a group of 69 patients with unknown primary sites and compared them with a group of 393 patients irradiated for carcinomas of the tonsillar region, supraglottic larynx, pharyngeal wall, and pyriform sinus (see Fig. 15-1). There was no difference in the risk of second primary tumors in the two groups.

One of the common radiation-induced neoplasms in the head and neck area is papillary carcinoma of the

TABLE 5-4. Multiple Simultaneous Head and Neck Cancers: Control of Disease Above the Clavicles and Survival (40 Patients)*

AJCC Stage	Patients	Excluded†	Control After Initial Treatment	Surgical Salvage		Ultimate Control	Absolute Disease-Free Survival		Cause-Specific 5-Year Survival
				Local	Neck		2-Year	5-Year	
I	2	0	2/2	0	0	2/2	2/2	1/1	1/1
II	8	1	5/7	1/2	0	6/7	6/8	2/6	2/4
III	10	1	2/9	2/3	0	4/9	4/10	1/9	1/7
IV	20	4	3/16	1/3	0/2	4/16	5/20	1/19	1/14
TOTAL	40	6	—	—	—	—	17/14	5/35	5/26

* Minimum follow-up of 2 years; range of 2 to 20 years.

† Died of intercurrent disease or distant metastasis within 2 years with above-clavicle control.

(McCollough WM, Million RR, Mendenhall WM, Parsons JT, Cassisi NJ. Treatment results for simultaneous primary squamous cell carcinomas of the head and neck. Laryngoscope 1988;98:81)

TABLE 5-5. Relative Risk of a New Primary Cancer Occurring After 5 Years According to Modality of Treatment of Squamous Cell Carcinoma: All Anatomic Sites (1163 Patients)

	Surgery (337 Patients)		Irradiation (720 Patients)		Preoperative or Postoperative Irradiation (106 Patients)	
Site	Patients	Percentage	Patients	Percentage	Patients	Percentage
Same location	6	1.8	20	2.8	2	1.9
Vicinity	14	4.2*	19	2.6*	7	6.6*
Remote sites in the oral covity and pharynx	16	4.7	39	5.4	8	7.5
Lung and esophagus	11†	3.3	39‡	5.4	6§	5.7

* Average incidence is 3.1% for the surgery and irradiation groups. This figure is statistically different from 6.6% (P = .07).

† 10 lung, 1 esophagus.

‡ 27 lung, 11 esophagus, 1 tracheo.

§ 4 lung, 2 esophagus.

Note: M. D. Anderson Hospital dota; patients treated January 1948 to December 1963; analysis August 1973.
(Kogelnik HE, Fletcher GH, Jesse RH. Clinical course of patients with squamous cell carcinoma of the upper respiratory and digestive tracts with no evidence of disease 5 years after initial treatment. Radiology 1975;115:424)

thyroid, which is a highly curable tumor. Radiation-induced sarcomas are almost never seen after high-dose irradiation of adults; the estimated lifetime risk is less than 1% for patients treated in the second decade and 3% to 5% for those treated in the first decade. Radiation-induced osteosarcoma and fibrosarcoma are frequently incurable, but even some of these patients are salvaged.[32] Sarcomas may occur in nonirradiated patients with retinoblastomas.

RISK OF LATE NECK RECURRENCE AND DISTANT METASTASIS AS A FACTOR IN TREATMENT DECISIONS

The risk of late-appearing (more than 5 years) neck disease and distant metastasis is shown in Table 5-6. There is no obvious difference comparing surgery, radiation therapy, and a combination of both.

TABLE 5-6. Incidence of Neck Disease and Distant Metastasis Appearing More Than 5 Years After Treatment in Patients With the Initial Primary Lesion and Neck Disease Controlled and No Squamous Cell Carcinoma Found Below the Clavicles: All Anatomic Sites (1163 Patients)

Modality of Treatment to the Primary Lesion	Incidence
Neck Disease	
Surgery	1.2% (4/337)
Irradiation	1.4% (10/720)
Combination surgery and irradiation	0% (0/106)
Distant Metastasis	
Surgery	1.2% (4/337)
Irradiation	0.6% (4/720)
Combination surgery and irradiation	2.8% (3/106)

Note: M. D. Anderson Hospital data; patients treated January 1948 to December 1965; analysis August 1973.
(Kogelnik HD, Fletcher GH, Jesse RH. Clinical course of patients with squamous cell carcinoma of the upper respiratory and digestive tracts with no evidence of disease 5 years after initial treatment. Radiology 1975;115:424)

RISK OF LATE-APPEARING COMPLICATIONS AS A FACTOR IN TREATMENT DECISIONS

Most surgical complications occur at or near the time of the operation. Late-appearing complications (eg, aspiration pneumonia after supraglottic laryngectomy) are relatively uncommon.

The rate of radiation therapy complications after 5 years is shown in Table 5-7. Most occur in patients with T2-3 lesions and are most significant for patients treated for oral cavity tumors.

INFLUENCE OF HISTOLOGY AND MORPHOLOGY ON TREATMENT DECISIONS (SQUAMOUS CELL CARCINOMA AND ITS VARIANTS)

Most malignant head and neck neoplasms arise from the surface epithelium and are, therefore, squamous cell carcinoma or one of its many variants, including lymphoepithelioma, spindle cell carcinoma, verrucous carcinoma, and undifferentiated carcinoma.

The less-differentiated tumors usually have a higher incidence of positive lymph nodes and a higher risk for distant metastasis than low-grade lesions of comparable size from similar anatomic sites. This factor is taken into consideration during treatment planning. The local and regional control of squamous cell carcinoma by radiation therapy is not much affected by grade, although the survival rate is lower for high-grade tumors because of the increased rate of distant metastasis. The presence of a lymphoid stroma (lymphoepithelioma) predicts better local–regional control and survival rates when treated by irradiation compared to garden-variety squamous cell carcinoma.

During a course of radiation therapy, the response rate or disappearance rate of high-grade carcinomas is usually more rapid than that of low-grade lesions. The physician is prone to label these rapidly responding tumors radiosensitive, but the rate of disappearance does not correlate in a linear fashion with radiocurability (see Chap. 12).

The gross and microscopic morphology or growth pattern plays a role in treatment results. Some squamous cell carcinomas tend to grow in an exophytic pattern with pushing borders; these lesions usually have a lower rate of lymph node metastasis and are more readily encompassed by an operation or by interstitial irradiation because the borders are well-defined and the chance of missing the margins during surgery or irradiation is low. These discrete lesions tend to respond better to treatment, whether they are managed by surgery, radiation therapy, or both.

Some squamous cell carcinomas (usually the poorly differentiated ones) tend to be markedly infiltrative, with fingers of tumor cells far beyond the visible or palpable lesion. This growth pattern is associated with a higher rate of regional lymph node metastasis and is generally more difficult to encompass by an operation. Because irradiation portals usually have a generous margin around the obvious lesion, it is less likely that the margins will be missed with radiation therapy, but control by radiation therapy alone is also less likely to be achieved for this growth pattern than for the more discrete lesions.

Differentiating between tumor recurrence and radiation necrosis after irradiation is not always easy. Because recurrence usually implies major ablation, the clinical picture must fit the diagnosis. Several examples of misdiagnosis of recurrent cancer have been seen in which the patient had a major cancer operation for recurrence, only to find that, in fact, the problem was a radiation necrosis that might have healed with conservative therapy. The opinion of a highly qualified pathologist is invaluable in avoiding such a situation.

Lymphoepithelioma

Lymphoepithelioma is a carcinoma with a lymphoid stroma. The lymphoid stroma may or may not be present in regional lymph nodes or distant metastases. Lymphoepithelioma occurs at anatomic sites that have lymphoid aggregates in the submucosa, namely, the na-

TABLE 5-7. Complications of Treatment Occurring After 5 Years in 720 Irradiated Patients With No Evidence of Disease at 5 Years

Site	Patients	Complications	Type of Complication				
			Soft Tissue Ulcers	Bone Necrosis	Excessive Fibrosis	Peripheral Neuropathy	Miscellaneous
Oral cavity and faucial arch	319	24 (7.5%)	10*	12*	1	1	0
Pharynx (nasopharynx, oropharynx, hypopharynx)	132	21 (15.9%)	1	3	5	8†	4
Larynx	252	2 (0.8%)	0	0	1	0	1
Nasal cavity and paranasal sinuses	17	0 (0%)	0	0	0	0	0

* One patient with additional fistula.

† One patient with bilateral neuropathy.

Note: M. D. Anderson Hospital data; patients treated January 1948 to December 1965; analysis August 1973.

(Kogelnik HD, Fletcher GH, Jesse RH. Clinical course of patients with squamous cell carcinoma of the upper respiratory and digestive tracts with no evidence of disease 5 years after initial treatment. Radiology 1975;115:425)

sopharynx, tonsil, and base of the tongue. It has a higher rate of cure by radiation therapy than squamous cell carcinoma.

Verrucous Carcinoma

Verrucous carcinoma is a "grade ½" squamous cell carcinoma that is most often found in the oral cavity, particularly on the gingiva and the buccal mucosa and the glottic larynx. It usually has an indolent growth pattern and is often associated with the chronic use of snuff or chewing tobacco. Verrucous tumors resemble warts: they are white or pink and exophytic, with distinct margins and multiple filiform processes that produce a roughened, cobblestone surface. The lesion may be soft or firm to palpation, depending on the degree of keratinization and associated inflammation. The pathologist may return a diagnosis of hyperkeratosis or pseudoepitheliomatous hyperplasia on a lesion that has the appearance of a cancer. Multiple biopsies usually are performed before the diagnosis is made. Eventually, cancer therapy may be recommended only because of the appearance of the lesion and observation of its continued growth. If the pathologist can readily make a diagnosis of carcinoma from histologic examination, the diagnosis of verrucous carcinoma is unlikely.

There is a great deal of controversy about the response of verrucous carcinoma to radiation therapy. Perez and coworkers[27] reported eight patients with verrucous carcinoma who were treated by irradiation; all eight tumors recurred. In three cases, the histologic picture evolved to a markedly undifferentiated picture.

Kraus and Perez-Mesa[14] reviewed 105 cases of verrucous carcinoma. Seventeen of the lesions were treated by radiation therapy, and all recurred. Four of the recurrences showed an anaplastic transformation, and all four patients died of metastatic disease. None of the surgically treated patients developed metastases.

Fonts and coworkers[6] reported 10 patients with verrucous carcinoma, but five patients actually had well-differentiated squamous cell carcinoma. Three patients developed anaplastic transformation; five patients were free of disease 1 to 3½ years after radiation therapy.

Although we have seen typical verrucous carcinomas disappear with radiation therapy and not recur during long periods of follow-up, it is our policy to select surgery for verrucous carcinoma whenever possible. We do not hesitate to try radiation therapy first if the morbidity (eg, from total laryngectomy) is unacceptable. Pathologists vary widely in the criteria they use to diagnose verrucous carcinoma, which probably explains some of the conflicting data. Many of the radiation therapy failures were treated with low-dose schemes. Nevertheless, prudence dictates the use of an operation when reasonable.

Spindle Cell Carcinoma

A component of spindle cells resembling sarcoma is intermixed with squamous cell carcinoma in an estimated 2% to 5% of malignant specimens taken from the upper aerodigestive tract. This picture is variously described in the literature as pleomorphic carcinoma, sarcomatoid squamous cell carcinoma, squamous cell carcinoma with spindle cell variant, pseudosarcoma, and spindle cell squamous cell carcinoma, among others. Most of these lesions cannot be distinguished grossly from the usual squamous cell carcinoma; a few are polyploid in appearance. In some, the spindle cell component is relatively minor; in others, it dominates the picture and the squamous cell component is difficult to find. The sarcomatoid component may have features that are consistent with malignant fibrohistiocytoma. The lymph node metastases may show only the spindle cell component, only the carcinomatous element, or a mixture of both. This pattern may be seen anywhere that squamous cell carcinoma is found in the head and neck area, but the oral cavity and larynx are the most common sites. Leventon and Evans[16] reported on 20 cases of spindle cell carcinoma. All of the patients with superficially invasive tumors were cured, whereas only 1 of the 10 patients with deep invasion was cured. The tumors responded both to surgery and radiation therapy, with 6 of the survivors being treated by operation, 3 by irradiation only, and 2 by combined treatment. Six of the tumors were said to have occurred in previously irradiated areas, and 5 of these patients eventually died of deeply invasive tumors. In general, the spindle cell element is disregarded in treatment decisions because there is a paucity of therapeutic information. It is important to inquire about a past history of irradiation.

Oat Cell Carcinoma

Oat cell carcinoma occurring in the head and neck has a similar biology as oat cell cancer of the lung. The treatment strategy of chemotherapy followed by radiation therapy is recommended.

GENERAL PRINCIPLES FOR MANAGEMENT OF THE PRIMARY SITE

> The recommended therapy depends to a large extent on which door the patient enters.
>
> *RR Million*

There are few generally accepted treatment recommendations for specific stages of squamous cell carcinomas of the head and neck.

Some institutions have a strong surgical bias; others have a strong radiotherapy bias. Specialists trained at these institutions tend to carry this bias into their professional careers. At the University of Florida, head and neck cancers are reviewed by a weekly multidisciplinary conference where the patients are examined and the radiographic and pathologic materials are reviewed. Treatment recommendations and sometimes alternative treatment plans are presented to the patient. This technique allows the patient and family a chance to make an informed selection of therapy. This book, then, reflects the philosophy of one institution.

Figure 5-1 shows the modified AJCC scheme for combining T stage and N stage into a total stage I to IV. Stage IV is subdivided into a relatively favorable group (IVA) and a very unfavorable group (IVB).[21] Patients with early-stage lesions (T1N0-1 or T2N0-1) usually have a favorable prognosis when managed by either surgery or radiation therapy, and combined treatment should be avoided because it only increases the morbidity and provides little or no benefit. Salvage is often achieved by a second procedure in the few instances of failure.

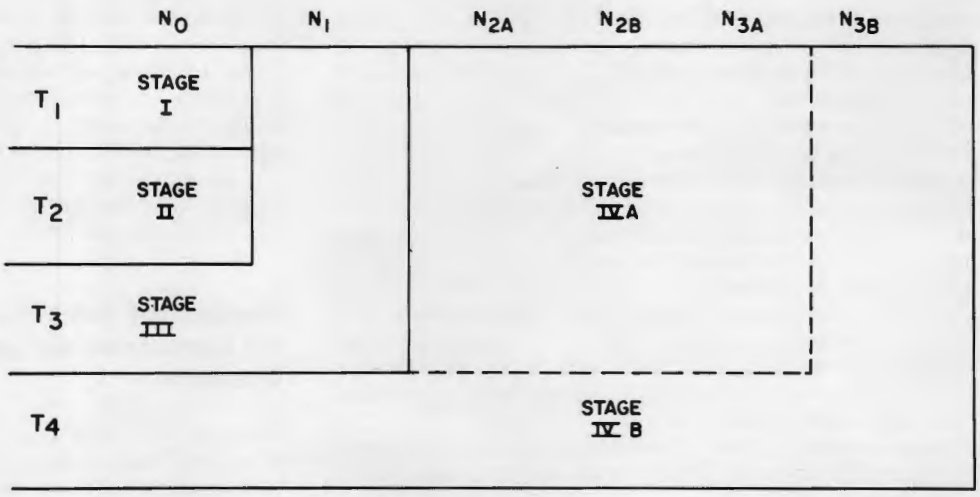

Figure 5-1. Modified AJCC stage classification. (Mendenhall WM, Parsons JT, Million RR, Cassisi NJ, Devine JW, Greene BD. A favorable subset of AJCC stage IV squamous cell carcinoma of the head and neck. Int J Radiol Oncol Biol Phys 1984;10:1842)

Patients with moderately advanced lesions may benefit from combined therapy in some instances, but if either radiation therapy or surgery is reasonably successful by itself, one modality may be held in reserve. When combined therapy is selected, it should be aggressive, because there is seldom a chance for salvage after combined approaches.

The most difficult decision is whether to offer a curative attempt to patients with very advanced lesions. There are always anecdotal cases of patients whose advanced disease was cured. However, at best, the cure rate for some very advanced lesions may be estimated at 1% to 2%. The question becomes, is it rational to put 100 patients through major therapy with a treatment-related mortality rate of 5% to 10% and a high morbidity to cure one or two patients? Many of these patients with very advanced lesions are in poor general medical condition, and treatment with radical surgery, radiation therapy, or both is simply unrealistic. However, if the patient is in relatively good condition, and especially if young, a curative approach may be considered. The patient and family must be presented the facts and assist in the decision. Frequently, when faced with a low-yield major ablative procedure, the patient selects a palliative course, usually radiation therapy. Chemotherapy may be used as the initial therapy in advanced cases to select those with responsive tumors who may also respond well to irradiation. Palliative surgery is used in selected cases to relieve major symptoms or reduce nursing care (eg, tracheostomy). There are patients with advanced disease for whom even a short course of palliative radiation therapy is considered inadvisable if symptoms can be controlled by other means. Experimental chemotherapy may be advised for advanced lesions, and often there is spectacular, if temporary, tumor regression. The best treatment may be only observation; 2% to 3% of patients seen in our clinic receive no cancer therapy, and 5% to 10% receive only palliative measures, usually a short course of radiation therapy.

Factors in the Selection of Patients for Irradiation

Prior high-dose irradiation to the head and neck area, even if given years previously, is usually a contraindication to radiation therapy, unless the new cancer is clearly out of the prior radiation portals. There are a few exceptions to this rule, such as recurrent lymphoepithelioma of the nasopharynx, but curative reirradiation is rarely successful and the risk of major necrosis is high. An operation should be the treatment of choice, with reirradiation used only in desperate or special circumstances.

A history of low-dose irradiation (eg, for acne) is a relative contraindication. The history of prior irradiation may be missed, because the irradiation was often given years ago. Irradiated skin has a characteristic appearance, and persistent questioning frequently confirms the suspicion. Radiation therapy records are usually not available, and one must depend on the appearance of the skin and mucosa to guess the possible radiation dose.

Most patients with squamous cell carcinoma either are or were confirmed tobacco or alcohol users. These patients are at a slightly greater risk to develop a radiation necrosis or edema if they continue their unsavory habits with zeal. However, if they moderate or stop smoking, drinking, or both, the risk of a complication is similar to that for other patients. The history of tobacco or alcohol use is not usually a decisive factor in treatment selection. The alcoholic is likely to refuse a major operation but is also rather intolerant of the acute side effects of irradiation once treatment is started. About 50% of the patients who smoke stop immediately when advised to do so, about 25% decrease their tobacco use, and the remaining 25% do not alter their habit.

A common reason for selecting radiation therapy instead of an operation is a concomitant medical condition. Radiation therapy has essentially a zero acute mortality rate, and it makes no sense to offer the patient an operation if the risk of an operative death is significant. Young patients are best treated by an operation, all other factors being equal, because the risk of a late-appearing radiation complication is ever present, especially for lesions of the oral cavity (see Table 5-7). Elderly or frail patients are frequently referred for radiation therapy even though they have a lesion preferably treated by an operation. A long, drawn-out, 6- to 7-week course of irradiation may be more wearing than an operation, which may entail a few days of hospitalization.

Bone and cartilage invasion are relative contraindications to radiation therapy.[23] There are numerous examples of benign and malignant bone tumors outside the

head and neck that may be cured by irradiation. Benign tumors that invade and destroy bone and cartilage in the head and neck area, such as chemodectomas and juvenile angiofibroma, may be cured by radiation therapy. Advanced lesions of the nasopharynx, nasal cavity, nasal vestibule, paranasal sinuses, middle ear, gingiva, larynx, hypopharynx, and skin that have invaded bone or cartilage have significant cure rates with acceptable morbidity. Surgical excision is often preferred for lesions with bone or cartilage invasion, particularly if the structure is expendable. However, almost all cases with cartilage and bone invasion are advanced and cure rates would not be expected to be great with any therapy. Minimal cartilage involvement in particular is not an ominous finding and occurs far more frequently than can be diagnosed by pretreatment studies.[2,3,5,8,11,19,20,22,25,26,28,29] A few patients have a fear of radiation therapy. If this fear is not easily reconciled, one should not force the issue.

Factors in the Selection of Patients for Surgery

> Make accurate incisions surrounding the whole tumor so as not to leave a single root.
>
> *Galen* (129 to 199 AD)

Many patients who present with head and neck malignancies are older, undernourished people who use alcohol and tobacco to excess. Medical problems such as diabetes, pulmonary disease, and cardiovascular disease are often present. All such factors must be considered and corrected before offering the choice of surgery to these patients. There are relatively few absolute contraindications to surgery, but if the medical problems are so severe that the risk with anesthesia is high, surgery is contraindicated unless there is no feasible alternative and the patient strongly urges that the operation be done. A myocardial infarction within the previous 3 months is a contraindication to surgery. A relative contraindication to surgery is the presence of simultaneous double primary lesions that cannot be encompassed in a single operative procedure; individualization is required for these cases.

The surgical goal in management of a primary lesion is complete excision with immediate reconstruction to a socially acceptable level of function and cosmesis. Surgery must be considered the therapeutic modality of choice if the cure rate is at least as great as with radiation therapy, if the functional and cosmetic deformities are acceptable to the patient, or if the anticipated complications from irradiation are severe enough to require surgery ultimately. The skills of the surgeon are a consideration; for instance, it would be better to treat an early lesion of the infrahyoid epiglottis with radiation therapy than with a total laryngectomy if the supraglottic laryngectomy is not in the surgeon's armamentarium, because a total laryngectomy is always an option for salvage.

Lesions in certain anatomic sites lend themselves to surgery with minimal morbidity (eg, small lesions of the lip, the lower gum and retromolar trigone, the tip of the tongue, the epiglottis, and the skin).

The surgeon must exercise prudent judgment in advising excision of advanced lesions. A few patients may be cured, but others may become functional or cosmetic cripples and wish they were dead. Some physicians justify their decision to perform excision with the attitude that "if we don't do something, the patient will die." These decisions vary with the experience and aggressiveness of the surgeon; the patient and his family must be totally informed of the probable chance of cure and the functional and cosmetic problems so that they may select the proper option. It is unwise to talk a patient into undergoing a major operative procedure only to have a bitter patient and family as a result of the effort.

Factors for the Selection of Patients for Combined Surgery and Radiation Therapy

The head and neck region is an area frequently treated by a combination of surgery and radiation therapy. Either preoperative or postoperative radiation therapy may be used, and there are advocates for each. Analysis of available data suggests that there is little or no difference in local–regional control or survival comparing the two sequences; the major differences are the increased operative morbidity associated with operations performed after radiation therapy and the higher doses of irradiation that can be used in the postoperative setting.

Combined modality therapy should be avoided when a high local–regional control rate (70% or greater) is predicted by either surgery or radiation therapy alone. In many patients who develop local or regional failure, salvage can be achieved by secondary procedures. As many as 15% to 20% die of other causes within 5 years, including 5% to 15% who develop another head and neck cancer within 5 years.

The advantages of postoperative compared with preoperative radiation therapy include less operative morbidity, more meaningful margin checks at the time of the operation, a knowledge of tumor spread for radiation treatment planning, safe use of a higher radiation dose, and tailoring of radiation dose and treatment volume based on surgical and pathologic findings and no chance that the patient will refuse surgery.

The disadvantages of postoperative radiation therapy include the larger treatment volume necessary to cover surgical dissections and scars, a delay to the start of radiation therapy with possible growth of tumor (especially contralateral neck nodes), and the higher dose required to accomplish the same rate of local–regional control.

Preoperative Radiation Therapy

Preoperative rather than postoperative radiation therapy is recommended for the following situations:

1. A trial dose of radiation therapy (5000 cGy) is given to judge the response of the primary lesion. The patient is reevaluated with the surgeon, and a decision is made to continue for cure by radiation therapy or to stop the irradiation and proceed in 4 to 6 weeks to an operation. This philosophy is selected for moderately advanced lesions that have a reasonable chance to respond favorably to radiation therapy, thereby avoiding a major ablative procedure. The pyriform sinus and larynx are common primary sites for use of this strategy. There is no proof that one can select patients on this basis, but the concept seems to work. In our practice, most patients selected for a trial complete a full course

of radiation therapy. On the other hand, a few patients initially selected for a full course of radiation therapy are reevaluated after 5000 cGy of treatment because the response is so poor, and irradiation is stopped and an operation is recommended.

2. A neck node that is on the borderline of resectability or inoperable is a reason to give radiation therapy before surgery. The dose to the primary lesion depends on whether it is to be treated for cure by radiation therapy or to be resected at the time of neck dissection. The neck mass receives a dose of 6000 to 8000 cGy. Lesser doses usually do not accomplish enough regression for complete resection. A reduced portal is used for the final boost. Most large nodes become resectable, and about half of the specimens contain no residual carcinoma. The control of the neck disease in this situation is respectable, and the complications are acceptable (see Chap. 6 for results of combined treatment to the neck). However, when the primary lesion is to be resected in addition to the neck nodes, the preoperative doses prescribed are tempered by the increased complications expected.
3. If reconstruction and rehabilitation will delay the start of postoperative radiation therapy by more than 12 weeks, preference may be given to the use of preoperative radiation therapy.
4. Simultaneous primary lesions are present.
5. Dermal invasion has occurred.
6. The patient has an unresectable primary tumor.

There are only a few clinical situations in which an unresectable primary lesion can be converted to a resectable lesion with preoperative radiation therapy. The full therapeutic dose is delivered in these cases before operation.

An unusual lesion in which radiation therapy was used to cure part of the primary lesion and surgery was used to resect only a portion of the lesion, thus necessitating "cutting across" an area that had been involved by cancer before irradiation, is shown in Figure 5-2.

The dose for preoperative radiation therapy is usually 5000 cGy over 5 to 6 weeks to the primary lesion; neck masses over 5 cm in diameter should receive a higher dose. Short treatment schemes using a few large fractions followed immediately by surgery have shown little or no advantage in comparison with surgery alone.[10,15,33] Moderate-dose schemes, 3000 to 4000 cGy, have not shown any great increase in control rates. A dose of 5000 cGy can control a large percentage of subclinical disease in lymph nodes and also reduce the recurrence rates for the primary site. A few venturesome groups have tried higher doses, 5500 to 6000 cGy to the primary site, but the morbidity may exceed the gain in cures (see Chap. 12 for further data on dose response).

TABLE 5-8. Preoperative Irradiation: Control Above the Clavicles at 5 Years According to Pathologic Findings* (116 Patients)

Site	Positive (%)	Negative (%)	*P* Value
Primary specimen	43	76	.004
Neck specimen	30	79	<.001
Surgical margins	28	58	.026
Perineural invasion	15	60	.001
Stage II or III	45	87	.058
Stage IV	43	68	.055
Oral cavity or oropharynx (37)	33	55	.26
Hypopharynx or larynx (79)	49	85	.01

* Product-limit method

Note: University of Florida data; patients treated October 1964 to December 1986; analysis January 1989 by Michael D. Sombeck, MD.

Sombeck reviewed 116 patients managed by preoperative radiation therapy at the University of Florida between 1964 and 1986 (Sombeck MD, unpublished data, January 1989). All patients had 2 years' minimum follow-up, and 94% were eligible for 5 years of follow-up. The indication for preoperative radiation therapy was trial of radiation therapy (32%), unresectable disease (30%), emergency tracheostomy (14%), physician preference (3%), or unclear reason (20%). Table 5-8 outlines the 5-year control rates according to the findings in the surgical specimen. The overall control rate above the clavicles was 40% for 37 patients with oral cavity or oropharynx lesions compared with 64% for 79 patients with hypopharynx or larynx primaries. The control rates are similar to those reported by the Radiation Therapy Oncology Group (RTOG)[13] and the State University of New York at Syracuse.[30,31] The interval from radiation therapy to operation, tumor differentiation, stage, estimated regression of primary lesion, and cartilage or bone invasion were not found to be prognostically significant.

Positive surgical margins, perineural invasion, and residual tumor in the specimen were significant findings predicting failure above the clavicles. There was a 6% operative mortality rate and an overall complication rate of 45%. Tables 5-9 and 5-10 compare results for three series.

TABLE 5-9. Preoperative Irradiation: Comparison of Rates of Control Above the Clavicles in Three Series

Site	University of Florida* (%)	RTOG[13] (%)	SUNY Syracuse[30,31] (%)
Oral cavity	43	48	
Oropharynx	33†	60	66
Hypopharynx and larynx			69
Hypopharynx	57	53	
Larynx	72	70	

* Sombeck MD, unpublished data, January 1989.

† Thirteen patients, all stage III or IV.

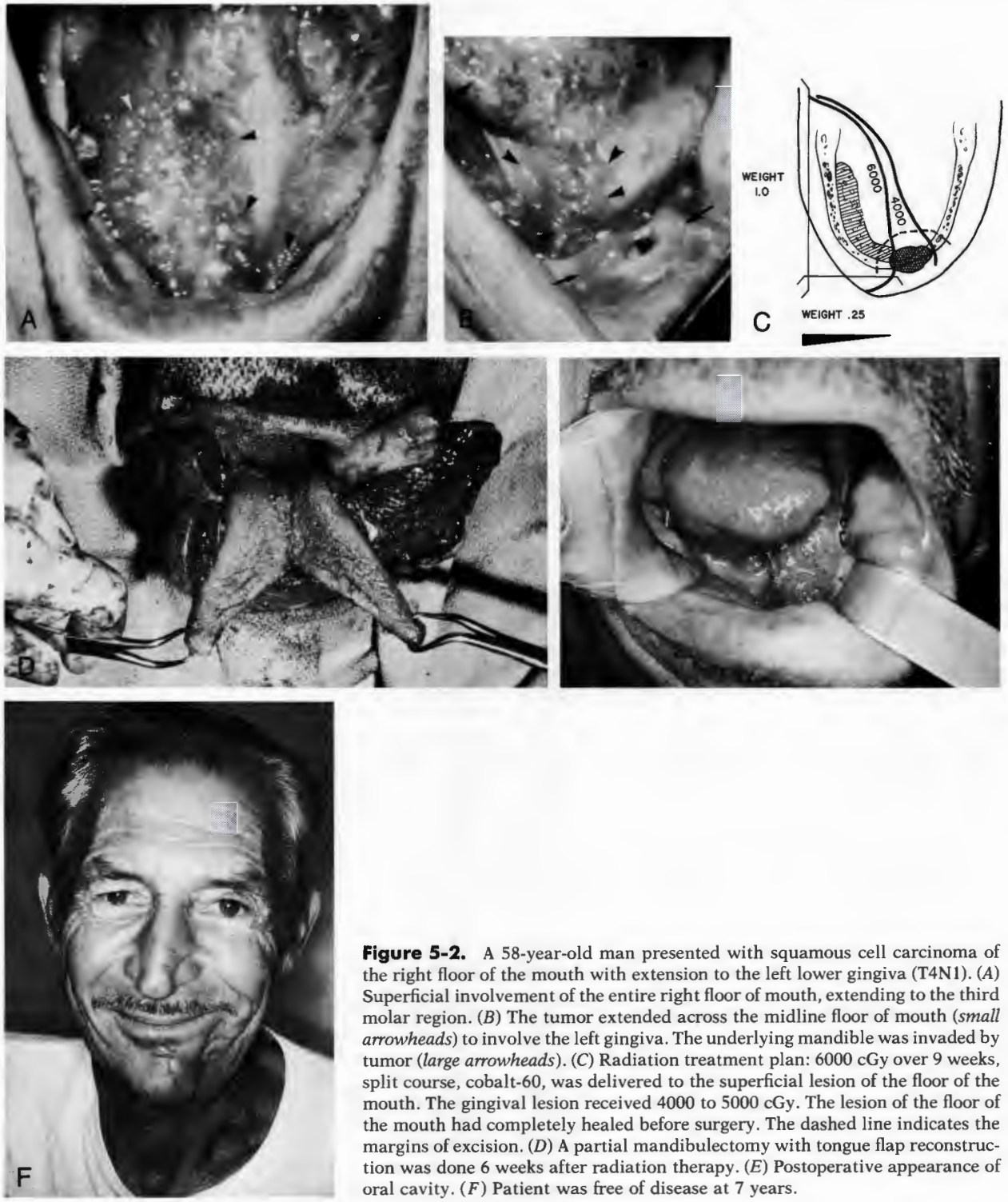

Figure 5-2. A 58-year-old man presented with squamous cell carcinoma of the right floor of the mouth with extension to the left lower gingiva (T4N1). (*A*) Superficial involvement of the entire right floor of mouth, extending to the third molar region. (*B*) The tumor extended across the midline floor of mouth (*small arrowheads*) to involve the left gingiva. The underlying mandible was invaded by tumor (*large arrowheads*). (*C*) Radiation treatment plan: 6000 cGy over 9 weeks, split course, cobalt-60, was delivered to the superficial lesion of the floor of the mouth. The gingival lesion received 4000 to 5000 cGy. The lesion of the floor of the mouth had completely healed before surgery. The dashed line indicates the margins of excision. (*D*) A partial mandibulectomy with tongue flap reconstruction was done 6 weeks after radiation therapy. (*E*) Postoperative appearance of oral cavity. (*F*) Patient was free of disease at 7 years.

TABLE 5-10. Preoperative Irradiation: Comparison of Cause-Specific Survival and Complication Rates in Three Series

Site	University of Florida* (%)	RTOG[13] (%)	SUNY Syracuse[30,31] (%)
Cause-specific survival (4 years)	43	40	51
Complications			
Overall	45	40	36
Fatal	6	4	?

* Sombeck MD, unpublished data, January 1989.

Postoperative Radiation Therapy

Postoperative radiation therapy is considered when the risk of recurrence above the clavicles exceeds 20%.

Ideally, the operative procedure should require only one stage and should be of such magnitude that irradiation is started within 3 months and preferably no later than 6 weeks after surgery. The operation should be undertaken only if it is believed to be highly likely that all gross disease will be removed and that margins will be negative. It is fashionable to talk about *debulking* or *cytoreductive* operations before radiation therapy. These terms have no precise meaning and should be avoided because they may imply partial removal of gross disease (cut-through), a maneuver that probably reduces the chance of control by radiation therapy rather than enhancing it.

The radiation therapist is frequently called on to decide further treatment based on the pathologist's report after surgery. Positive margins or close margins are definitely an indication for radiation therapy, but the failure rate with negative margins is substantial. Looser and coworkers[17] compared the clinical significance of negative and positive margins for 1775 previously untreated squamous cell carcinomas of the head and neck (excluding glottic and skin). Only 3.5% were scored as having positive margins. The incidence of recurrence at the primary site was 31.7% for patients with negative margins and 71% for those with positive margins. There was no difference whether the positive margin was due to carcinoma in situ, invasive tumor, or close margin (within 5 mm). Other indications for postoperative irradiation may be cartilage or bone invasion, extension into the skin or soft tissues of the neck, perineural spread, and high-grade histology. Margins initially positive at the time of operation are an indication for postoperative irradiation even if subsequent margins are negative for tumor. Specific indications relate to each primary site and are described in the specific anatomic chapter in this book.

The findings in the neck dissection are frequently the indication for postoperative radiation therapy. If there are more than two positive nodes, positive nodes at different levels in the neck, invasion through the capsule, or

TABLE 5-11. Postoperative Irradiation: Location of Recurrences Above the Clavicles (25 Patients)*

Location	Supraglottic Larynx (28)	Glottic Larynx (25)	Hypopharynx (17)	Oropharynx (5)	Oral Tongue (8)	Floor of Mouth (9)	Retromolar Trigone (15)	Gingiva (1)	Total (108)
Primary field									21 (84%)
Mucosal	2	0	0	0	2	0	2	0	
Nodal	1	2	1	0	0	1	0	0	
Soft tissues of neck	1	1	1	1	1	2	1	1	
Under midline block	1†‡	0	0	0	0	0	0	0	
Posterior cervical field									2 (8%)
Field edge	0	0	1§	0	1#	0	0	0	
Low neck field									2 (8%)
Stomal	0	1¶	0	0	0	0	0	0	
Under midline laryngeal block	0	0	0	0	0	1‡	0	0	

* Numbers in parentheses in headings indicate number of patients at risk for each site.

† After supraglottic laryngectomy, patient was treated only to the neck by way of anterior and posterior fields with the midline shielded.

‡ Soft tissue recurrence in an area that received less than 1000 cGy.

§ Nodal tissue recurrence in area that received 5000 cGy.

Soft tissue recurrence in area that received approximately 4700 cGy.

¶ Tumor extended more than 5 mm subglottically; stoma received 6000 cGy.

(Amdur RJ, Parsons JT, Mendenhall WM, Million RR, Stringer SP, Cassisi NJ. Postoperative irradiation for squamous cell carcinoma of the head and neck: an analysis of treatment results and complications. Int J Radiat Oncol Biol Phys 1989;16:29)

high-grade histology, then a significant risk of recurrence in both the dissected neck and the contralateral neck can be predicted.

The referring surgeon is sometimes insistent that the patient receive postoperative radiation therapy, even though there is no obvious indication for it; it is usually best to follow the surgeon's intuition (see Chap. 12 for full discussion of the results of postoperative radiation therapy).

Amdur and associates[1] reviewed the results for 134 patients with squamous cell carcinoma of oral cavity, oropharynx, larynx, or hypopharynx managed by surgery and postoperative radiation therapy between 1964 and 1984. Ninety-six were stage III or IV. The overall local–regional control of disease above the clavicles was 77% for 108 evaluable patients. All but one failure occurred before 2 years. Table 5-11 shows the location of the failure related to the radiation portals; 84% of failures occurred in the primary portals (ie, primary site and adjacent neck). It is sometimes a moot point whether recurrences developing in the neck in or near the surgical scar are an implant from the primary lesion or a neck recurrence. The rate of control was related to surgical margin as shown in Figure 5-3. The control rate was poorer for oral cavity than the other sites (Table 5-12). The rate of control above the clavicles according to the number of indications for postoperative radiation therapy is shown in Table 5-13. The interval between surgery and irradiation up to 10 weeks did not affect the control rate. Survival (life-table method) is shown according to surgical margin in Figure 5-4. The severe complications are listed in Table 5-14 according to the number of patients at risk for each particular complication. In Table 5-15, the University of Florida series is compared with two surgical series.

(*text continues on page 74*)

TABLE 5-12. Postoperative Irradiation: Control Related to Margin and Anatomic Site

Site	Control Above the Clavicles	
	Negative Margins	Invasive Cancer at Margin
Oral cavity	21/28 (75%)	0/5
Oropharynx, larynx, hypopharynx	54/64 (84%)	8/11 (73%)
P value	.22	.013

Note: University of Florida data; patients treated October 1964 to October 1984; analysis December 1986 by Robert J. Amdur, MD.

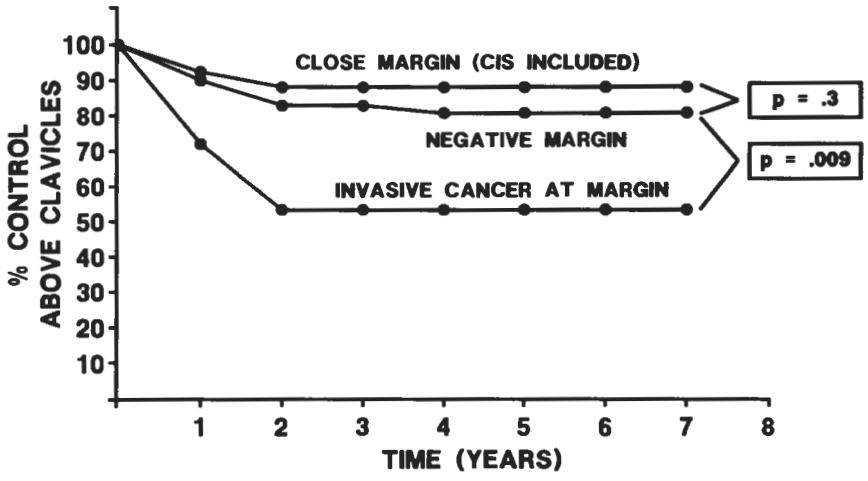

Figure 5-3. Postoperative irradiation: Control above the clavicles (life-table method) by surgical margin. For close margin (carcinoma in situ included) versus negative margin, $P = 3$. For negative margin versus invasive cancer at the margin, $P = .009$. (Amdur RJ, Parsons JT, Mendenhall WM, Million RR, Stringer SP, Cassisi NJ. Postoperative irradiation for squamous cell carcinoma of the head and neck: an analysis of the treatment results and complications. Int J Radiat Oncol Biol Phys 1989;16:30)

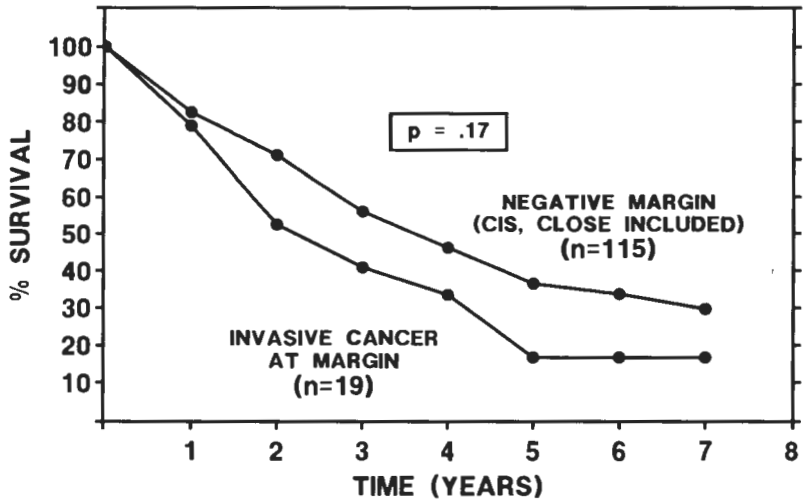

Figure 5-4. Postoperative irradiation: Survival (life-table method) by surgical margin. CIS, carcinoma in situ. (Amdur RJ, Parsons JT, Mendenhall WM, Million RR, Stringer SP, Cassisi NJ. Postoperative irradiation for squamous cell carcinoma of the head and neck: an analysis of the treatment results and complications. Int J Radiat Oncol Biol Phys 1989;16:33)

TABLE 5-13. Postoperative Irradiation: Control Related to Number of Indications for Radiotherapy

	Control Above the Clavicles	
Margins	1–3 Indications	≥4 Indications
Negative, close, carcinoma in situ	67/79 (85%)	8/13 (62%)
Invasive cancer	5/10	3/6

Note: University of Florida data.
(Amdur RJ, Parsons JT, Mendenhall WM, Million RR, Stringer SP, Cassisi NJ. Postoperative irradiation for squamous cell carcinoma of the head and neck: an analysis of treatment results and complications. Int J Radiat Oncol Biol Phys 1989;16:25–36)

TABLE 5-14. Postoperative Irradiation: Severe Complications of Combined Therapy

Dose (cGy)	Pharyngeal Stricture (91 Patients)*	Stomal Stenosis (84 Potients)*	Intraoral Bone or Soft Tissue Necrosis (43 Patients)*	Laryngeal Edema (7 Patients)*	Infection Fistula (15 Patients)*
<5000	0/4	0/16	0	0/1	0/4
5000–5900	2/20	0/37	1/2	0/1	0/22
6000–6500	1/48	0/29	0/19	1/5	0/63
>6500	0/19	1/2	1/22	0	2/26
TOTAL	3/91 (3%)†	1/84 (1%)‡	2/43 (5%)§	1/7 (14%)#	2/115 (2%)¶

* See text.
† All three required gastrostomy tube until death (7–34 months after radiation therapy).
‡ Required surgical revision.
§ One mandibular exposure required operative debridement (5700 cGy) and one tongue necrosis required partial glossectomy (7000 cGy).
# Required temporary tracheostomy 3 years after radiation therapy; resolved within 6 months.
¶ One fistula required multiple operations and one infection led to mandibular tray removal.
(Amdur RJ, Parsons JT, Mendenhall WM, Million RR, Stringer SP, Cassisi NJ. Postoperative irradiation for squamous cell carcinoma of the head and neck: an analysis of treatment results and complications. Int J Radiat Oncol Biol Phys 1989;16:33)

TABLE 5-15. Postoperative Irradiation: Comparison of Rate of Recurrence at the Primary Site for Three Series*

Status of Surgical Margin	Surgery Plus Radiation Therapy (University of Florida)	Surgery Alone	
		Roswell Park[4]	Memorial Hospital[17]
Negative	8/70 (11%)	40/234 (17%)	534/1713 (31%)
Close (≤5 mm)	1/19 (5%)	4/10 (40%)	14/19 (74%)
Carcinoma in situ	1/3 (33%)	1/2 (50%)	11/13 (85%)
Invasive cancer	6/16 (38%)	12/22 (55%)	16/25 (64%)

* In the University of Florida study,[1] 4% of patients had stage I or II disease, compared with 47% in the series by Chen and colleagues.[4] In the series reported by Looser and coworkers,[17] stratification by stage was not given for the entire patient population, but for patients with nonnegative margins, 32% had stage I or II disease.
(Amdur RJ, Parsons JT, Mendenhall WM, Million RR, Stringer SP, Cassisi NJ. Postoperative irradiation for squamous cell carcinoma of the head and neck: an analysis of treatment results and complications. Int J Radiat Oncol Biol Phys 1989;16:35)

Some patients have prolonged healing problems and concomitant indications for radiation therapy. Nineteen patients were irradiated with open wounds. The wounds healed in 13 within 6 months with conservative management. Six were not healed 7 to 34 months after irradiation therapy. Each situation is individualized, but it may be necessary to start irradiation before complete healing if there are major indications for radiation therapy.[9]

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6

MANAGEMENT OF THE NECK FOR SQUAMOUS CELL CARCINOMA

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Management of squamous cell carcinoma that involves the neck lymph nodes is closely tied to management of the primary lesion; however, certain general principles can be outlined. Death due only to failure to control metastatic tumor in the neck if the primary tumor is controlled should be an uncommon event if surgery and radiation therapy are used to maximum advantage. Variations in the management of the neck according to the primary site and other histologies are discussed under specific anatomic chapters.

ANATOMY OF THE LYMPHATIC SYSTEM OF THE HEAD AND NECK

The lymphatic system arises embryonically by a budding from the venous system, which explains the close anatomic association of the two systems. One of the normal functions of the lymphatic system is to reabsorb the large protein molecules and lymphocytes from the interstitial space and return them to the bloodstream. The blood capillaries have narrow endothelial junctions and do not normally reabsorb large molecules and lymphocytes. The capillary lymphatics, on the other hand, have relatively open endothelial junctions that permit the larger molecules to be absorbed, and this probably explains why tumor cells enter the lymphatic system more readily than the vascular system.

Capillary Lymphatics

Capillary lymphatics originate as a closed cul-de-sac; the efferent vessels anastomose to form a network of lymph vessels. There are no capillary lymphatics in the epithelium, central nervous system (CNS), perineurium or nerves, cartilage, bone, bone marrow, eyeball, membranous labyrinth, or placenta.[119,142] Muscle and fat contain few capillary lymphatics. There are a few capillary lymphatics in the periosteum or perichondrium but none within bone and cartilage. The fact that there are no capillary lymphatics in the eyeball and few within the orbit explains the low rate of lymphatic metastases for tumors arising in orbital tissues.[119] The perineural space is not a part of the lymphatic system and does not communicate with the lymphatic system.[65]

Because there are no capillary lymphatics in the epithelium, a tumor must penetrate the lamina propria before lymphatic invasion can occur. In the mucosa and skin, the blood capillaries are generally closer to the surface than the lymphatic capillaries; in the superficial tissues, the lymphatic capillaries are usually finer in diameter than in the deeper layers. Recent histologic studies have shown a relation between depth of squamous cell carcinoma invasion and the risk of lymph node metastases.[98,129] Similar observations have been refined for malignant melanoma of the skin. The density of the capillary network in any given head and neck site may be predicted by the relative incidence of lymph node metas-

tases. The density of the capillary lymphatic network does not necessarily correspond to the density of the vascular capillary system. The nasopharynx and pyriform sinus have the most profuse networks of capillary lymphatics. The paranasal sinuses, middle ear, and vocal cord have essentially no capillary lymphatics, which is in agreement with the nearly zero rate of lymph node metastasis when tumor is confined to these sites. The capillary lymphatic system, particularly in the larynx and trachea, atrophies with age.

Lymphatic Trunks

The capillary lymphatics converge to form lymphatic trunks. The superficial skin lymphatic vessels lie in the outer two thirds of the dermis and are without valves; once cancer invades this system, flow may be unpredictable and erratic, with satellite skin nodules surfacing at remote distances from the original area of skin invasion. The deeper skin lymphatic vessels have valves and lie in the inner layer of dermis and the superficial subcutaneous layer. Lymphatic vessels draining the mucous membranes have valves. The lymphatic trunks eventually empty into a large vein, usually near the junction of the internal jugular vein and the subclavian vein, the so-called venous angle. However, the lymphatic vessels, particularly those of the thyroid, may, on occasion, empty directly into the internal jugular vein or subclavian vein well above the venous angle. Lymphaticovenous connections exist between lymphatic trunks and veins or within the lymph node. The lymphaticovenous connections between vessels are probably of little importance until a lymphatic trunk is obstructed but are occasionally observed in otherwise normal lymphangiograms. The lymphatic trunks do not have an absorbing function, only a transporting function. The direction of lymphatic flow for each anatomic site is generally predictable and is outlined as each site is discussed in later chapters; aberrant pathways may occur, however. Tiny intercalated lymph nodes may occur anywhere along a lymph vessel. Obstruction of a lymph vessel has the effect of rerouting the lymphatic flow. Complete obstruction by surgical transection may cause major changes in the expected pathway of lymph node metastasis. Radiation therapy causes partial obstruction, and the degree of obstruction is dose-dependent. Lymph nodes that are replaced by tumor may cause partial or complete obstruction and detour the normal flow.

Lymph Nodes

There are an estimated 150 to 350 lymph nodes above the clavicles, nearly one third of the total lymph nodes in the body. The arrangement of the lymph nodes in the head and neck region is shown in Figure 6-1.[119] The nomenclature associated with the cervical lymph nodes is burdened by a variety of synonyms, some of which are listed in Table 6-1. The normal cervical lymphatics as shown by lymphangiography are depicted in Figures 6-2 through 6-4.[36] The normal internal jugular vein is shown in Figure 6-5.[36]

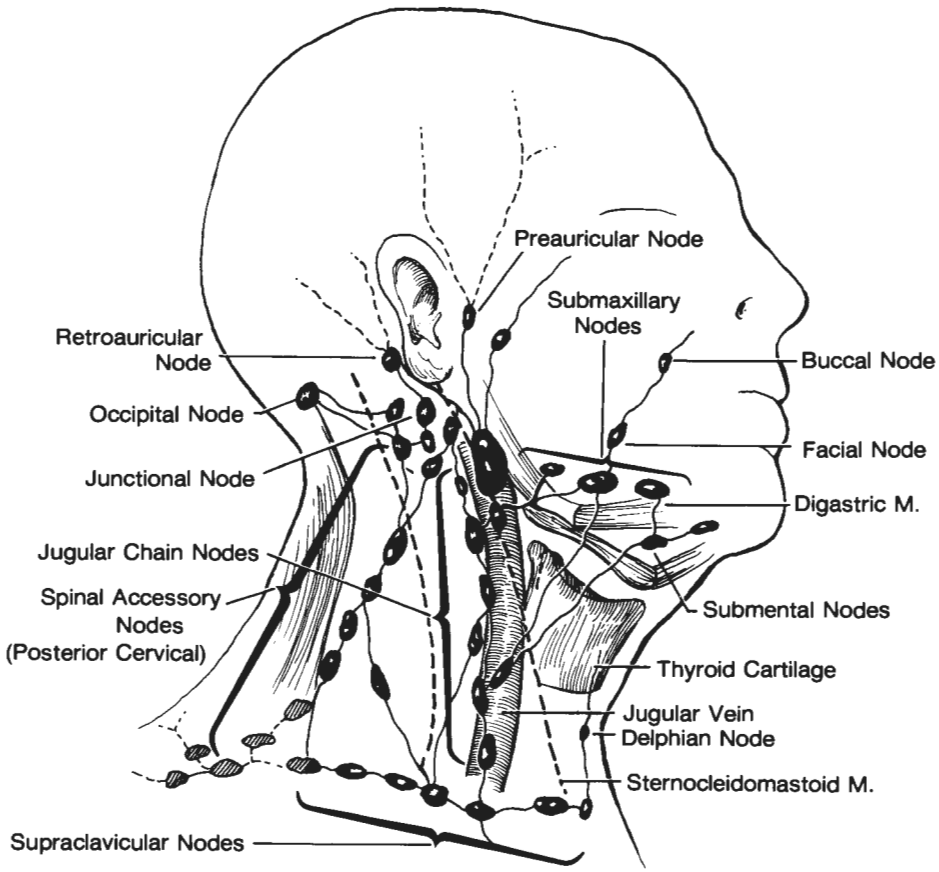

Figure 6-1. Arrangement of lymph nodes in the head and neck. (Redrawn from Rouvière H. Anatomy of the human lymphatic system. Tobias MJ [trans]. Ann Arbor, MI, Edwards Brothers, 1938:27)

TABLE 6-1. Synonyms for Names of Cervical Lymph Node Chains

Name Used in This Text	Synonym
Internal jugular chain (8–32 nodes)	Deep cervical chain
Spinal accessory chain (6–10 nodes)	Posterior cervical nodes
Supraclavicular nodes	Transverse cervical chain
Junctional nodes	Parapharyngeal nodes Superior or high internal jugular vein nodes
Submandibular	Submaxillary
Subdigastric nodes (1–5 nodes in adults)	Tonsillar node Principal node (of Küttner) Jugulodigstric nodes
Middle jugular chain	Omohyoid nodes
Lower jugular chain	—
Lateral retropharyngeal node	Node of Rouvière
Retroauricular nodes	Mastoid nodes

The intercalated lymph nodes are inconstant, minute, 1- to 2-mm lymph nodes that occur along the course of a lymph vessel between its origin and its entrance to a larger lymph node. When these nodes become involved and replaced by tumor, they might be misdiagnosed as satellite nodules.

The jugular lymph nodes are aligned in relation to the internal jugular vein from the jugular fossa at the base of the skull to the termination of its lymphatic trunks at the base of the neck. The highest jugular nodes lie near the base of the skull in the poststyloid portion of the lateral pharyngeal (parapharyngeal) space and are referred to as the junctional lymph nodes. They lie deep to the sternocleidomastoid muscle, the posterior belly of the digastric muscle, and the tail of the parotid and are often difficult to detect by physical examination, even when enlarged (Fig. 6-6). These lymph nodes form an extensive lymphoid aggregate. They are often referred to as the parapharyngeal lymph nodes, because they occupy the parapharyngeal space. The term *junctional lymph nodes* derives from the junction of the spinal accessory and internal jugular lymphatic chains.

The remainder of the internal jugular vein lymph nodes are arbitrarily divided into upper, middle, and lower. The upper group begins at the lower border of the posterior belly of the digastric muscle and is referred to as the *subdigastric lymph nodes.* Virtually all head and neck malignancies spread to the subdigastric area, either primarily or secondarily. The subdigastric nodes lie anterior or lateral to the internal jugular vein and may be palpated just in front of the sternocleidomastoid muscle or deep to the muscle. One of the subdigastric lymph nodes, the principal node, is normally large and elliptical and can be detected in most people even when normal. The midjugular lymph nodes lie deep to the sternocleidomastoid at a level between the thyroid notch and the cricoid cartilage. The low jugular nodes assume a more anterior and medial relation to the jugular vein and lie close to the trachea; these nodes are fewer and less constant than the upper and middle jugular lymph nodes.

The lymph nodes of the spinal accessory chain (usually six to ten nodes) are distributed along the general course of the spinal accessory nerve. The superior nodes

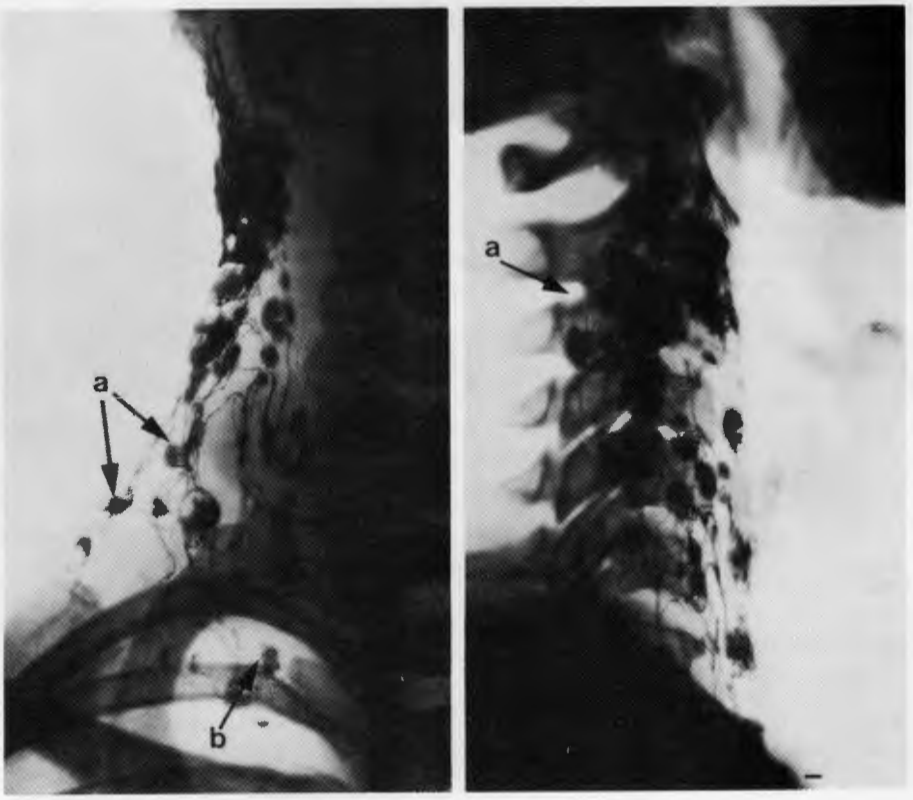

Figure 6-2. Normal cervical lymphatics as shown by lymphangiography. Early filling image shows contrast still in lymphatic trunks. The beaded appearance of the lymphatic trunks is due to the semilunar valves. a, Spinal accessory lymph nodes; b, supraclavicular lymph nodes. (Fisch U. Lymphographische Untersuchungen über das zervikale Lymphsystem [Fortschritte der Hals-Nasen-Ohren-heilkunde, vol 14]. Basel, Karger, 1966:53)

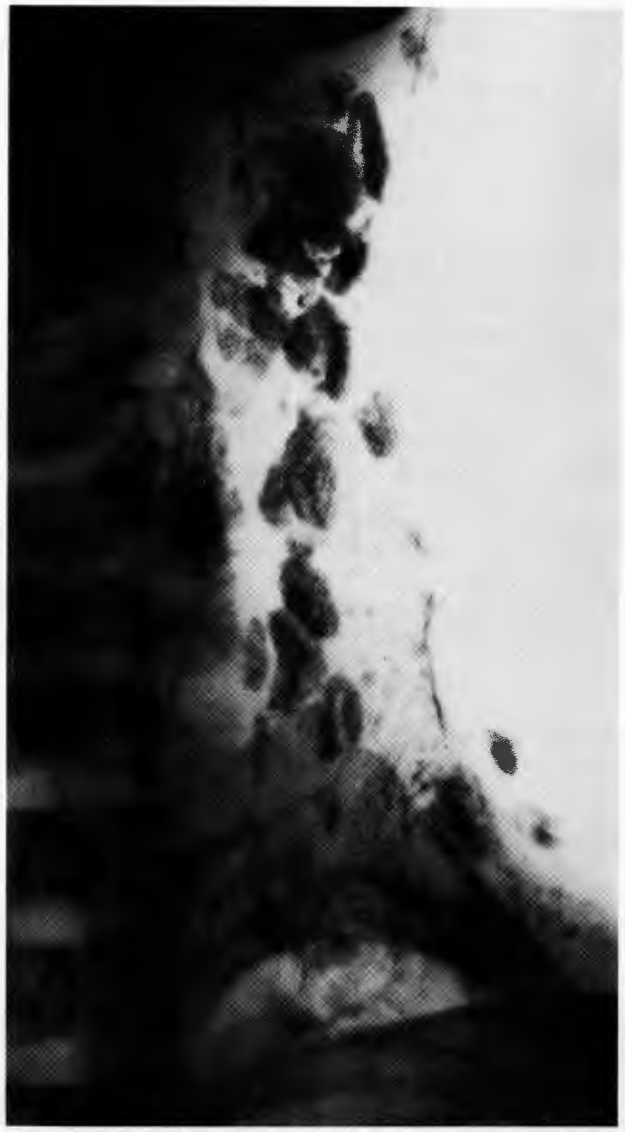

Figure 6-3. Normal cervical lymphangiogram, late image. Twenty-three lymph nodes were counted between the mastoid tip and hyoid bone. (Fisch U. Lymphographische Untersuchungen über das zervikale Lymphsystem [Forschritte der Hals-Nasen-Ohrenheilkunde, vol 14]. Basel, Karger, 1966:66)

of the spinal accessory chain blend with the upper internal jugular vein lymph nodes. The middle and lower spinal accessory chain nodes diverge posteriorly and become continuous with the supraclavicular chain. They are covered only by the skin and thin platysma muscle.

The supraclavicular lymph nodes lie in the lower neck along the upper margin of the clavicle and communicate with the spinal accessory chain. They are actually a continuation of part of the axillary chain and join other efferent trunks from the axilla before ending in the venous angle. They receive lymph from the head and neck, the ipsilateral upper extremity, the breast, the thorax, and the abdomen.

The submandibular lymph nodes (three to six in number) are related to the submandibular salivary gland, the undersurface of the mandible, and the anterior facial vein. These lymph nodes drain the lips, floor of the mouth, buccal mucosa, upper and lower gums, nasal vestibule, skin of the anterior face including the medial eyelids, oral tongue, palate, and submandibular and sublingual salivary glands.

The submental lymph nodes lie in the midline between the anterior bellies of the digastric muscles and between the hyoid bone and symphysis menti; they are external to the mylohyoid muscle. They receive lymph from the lip, chin, and cheeks and, to a lesser extent, from the floor of the mouth, anterior lower gingiva, and tip of the tongue. The efferent vessels drain to the submandibular or subdigastric lymph nodes.

Figure 6-4. Normal cervical lymphangiogram. Note the relation of the spinal accessory lymph nodes (*arrows*) to the spinous processes. (Fisch U. Lymphographische Untersuchungen über das zervikale Lymphsystem [Forschritte der Hals-Nasen-Ohrenheilkunde, vol 14]. Basel, Karger, 1966:70)

Figure 6-5. Anteroposterior (*A*) and lateral (*B*) roentgenograms of the internal jugular vein. Compare relation of the internal jugular vein with the cervical lymph nodes in Figures 6-3 through 6-5. (Fisch U. Lymphographische Untersuchungen über das zervikale Lymphsystem [Forschritte der Hals-Nasen-Ohrenheilkunde, vol 14]. Basel, Karger, 1966:67)

The occipital lymph nodes (one to six in number) receive lymph from the occipital scalp and the skin of the upper nape of the neck. The nodes lie in the posterior midline and laterally in the angle formed by the sternocleidomastoid muscle and trapezius muscle insertions.

The retroauricular nodes (one or two in number when present) are located behind the pinna in relation to the mastoid bone. They receive lymph vessels from the parietal scalp and skin of the ear.

The parotid area lymph nodes are divided into the lymph nodes within the fascia of the parotid gland and the preauricular lymph nodes outside the parotid fascia (Fig. 6-7). A discussion of the parotid gland lymph nodes is presented in Chapter 27. The preauricular lymph nodes (one to four in number when present) lie superficial to the parotid fascia in close relation to the pinna and the superficial temporal vessels. They are important in the spread of skin cancer and in lymphomas. They receive lymph from the skin of the frontal scalp, temple area, and nose, eyelids, pinna, external auditory canal, and malar area. There is a pathway for drainage of the eustachian tube to these nodes.[119]

The facial nodes are inconstant, intercalated lymph nodes located in the subcutaneous tissues along the general course of the anterior facial artery and vein and their branches. They are subclassified by Rouvière[119] into inferior maxillary, infraorbital, buccinator, and malar. The inferior maxillary (mandibular) nodes lie lateral to the mandible and near the mental foramen. The buccinator group is located in the subcutaneous tissue about 2 to 3 cm behind the angle of the mouth and in the vicinity of the entry of Stensen's duct into the buccinator muscle. The infraorbital node lies near the canine fossa.[50] The malar node lies over the zygomatic process of the maxilla in the subcutaneous tissue lateral to the lateral canthus.

A lymph node or nodes, not previously described, that lie deep to the zygomatic process of the maxilla in the lower portion of the infratemporal fossa have been diagnosed by CT scan on three occasions (see Fig. 6-7*C*, retrozygomatic node). The node was involved by cancer that had spread from the retromolar trigone in two cases and from the nasal region in one case.

The lingual lymph nodes are found in the oral tongue, located along the lymph vessels of the tongue. The median lingual lymph nodes are located between the lingual septum and the medial side of the genioglossus muscle. The lateral lingual lymph nodes lie on the lateral aspect of the genioglossus or on the hyoglossus muscle along the lingual artery and vein; they are in direct relation to the sublingual glands (Fig. 6-8).[105] The lateral lingual lymph nodes were found in 30% and the medial in 15% of fetal and neonatal cadavers.[63]

The lateral retropharyngeal lymph nodes lie external to the pharyngeal constrictor muscle and lateral to the anterior rectus capitis muscle and fascia and anterior to the lateral masses of C1 and occasionally C2 (see Fig. 6-6). The internal carotid artery and the upper pole of the superior cervical ganglion of the sympathetic chain lie just lateral to these nodes and are separated from the nodes only by a layer of fascia. These nodes atrophy with age. They receive lymph from the nasal cavity, nasopharynx, pharyngeal walls, pyriform sinus, hard and soft palate, middle ear, and eustachian tube.

The medial retropharyngeal lymph nodes are tiny, inconstant, intercalated nodes that lie near the midline of the posterior pharyngeal wall between the pharyngeal constrictor and the rectus capitis muscles and range from C1 to the level of the hyoid but usually fall at the C1 level.

The paratracheal lymph nodes may be divided into an anterior midline group and a lateral group (Fig. 6-9).[73]

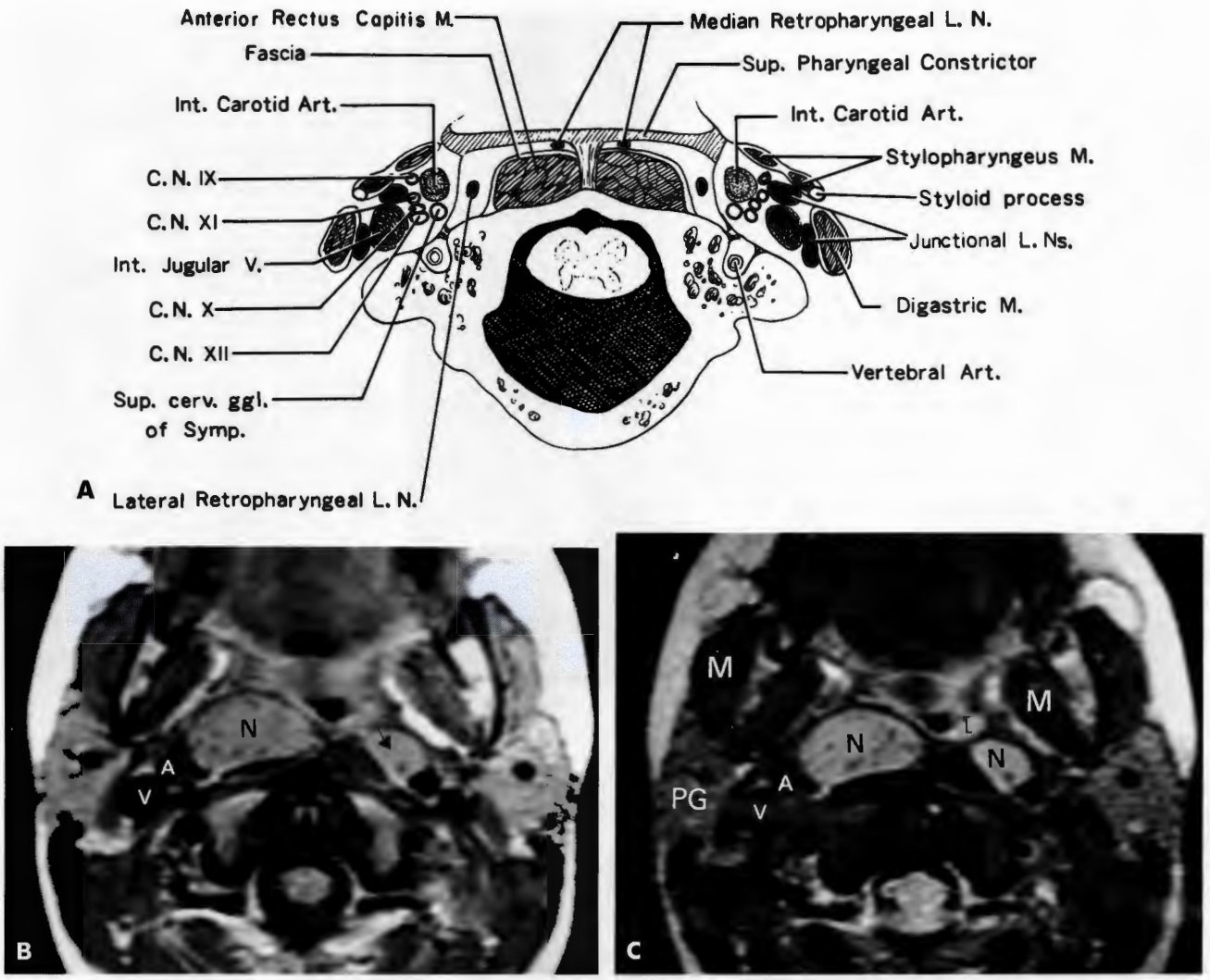

Figure 6-6. (*A*) Anatomic relations of junctional and retropharyngeal lymph nodes. (*B*) MRI study shows an enlarged, reactive retropharyngeal lymph node (N) in a child. The node lies medial to the carotid artery (A) and jugular vein (V). A more normal-sized retropharyngeal node (arrow) is present on the opposite side. (*C*) A heavily T2-weighted image shows that the nodes (N) retain a relatively high signal compared to surrounding muscles (M) and the parotid gland (PG). The nodes being lymphoid tissue have a signal intensity virtually identical to that of the lymphoid tissue lining the lower nasopharynx.

The small anterior midline lymph nodes are referred to as *prelaryngeal, prethyroid,* or *pretracheal* according to their position. The prelaryngeal nodes are usually located in relation to the cricothyroid membrane but may be above or below this site. They are seen on whole organ sections and are small when normal or even when replaced by tumor.[104] The largest one seen clinically was 1.5 cm in diameter, and they are usually 2 to 3 mm in diameter when palpable. The midline prelaryngeal node is often referred to as the Delphian node* because when involved by tumor it was said to herald bad news (oracle of Delphi).[25] The Delphian node receives lymph from the upper anterior portion of the body of both thyroid lobes, from the upper poles, and from the isthmus. It also receives lymph from the larynx, particularly the subglottic larynx.

The lateral paratracheal lymph nodes (recurrent chain) lie in the groove between the trachea and esophagus along the recurrent laryngeal nerve. These lymph nodes are surrounded by loose fatty tissue, which makes

* The first nodes to be exposed at the time of surgery for thyroid carcinoma are the midline lymph nodes anterior to the larynx and trachea. There is always one node in the midline in relationship to the thyrocricoid area, commonly two or three, occasionally four. This node or group of nodes was termed *Delphian node* by Dr. Oliver Cope because it is exposed first and, if diseased, foretells the nature of the disease process to be found in the thyroid gland. The name Delphian was suggested to Dr. Cope by Dr. Raymond V. Randall, then a fourth-year medical student at Harvard Medical School attending the Thyroid Clinic at Massachusetts General Hospital.[25]

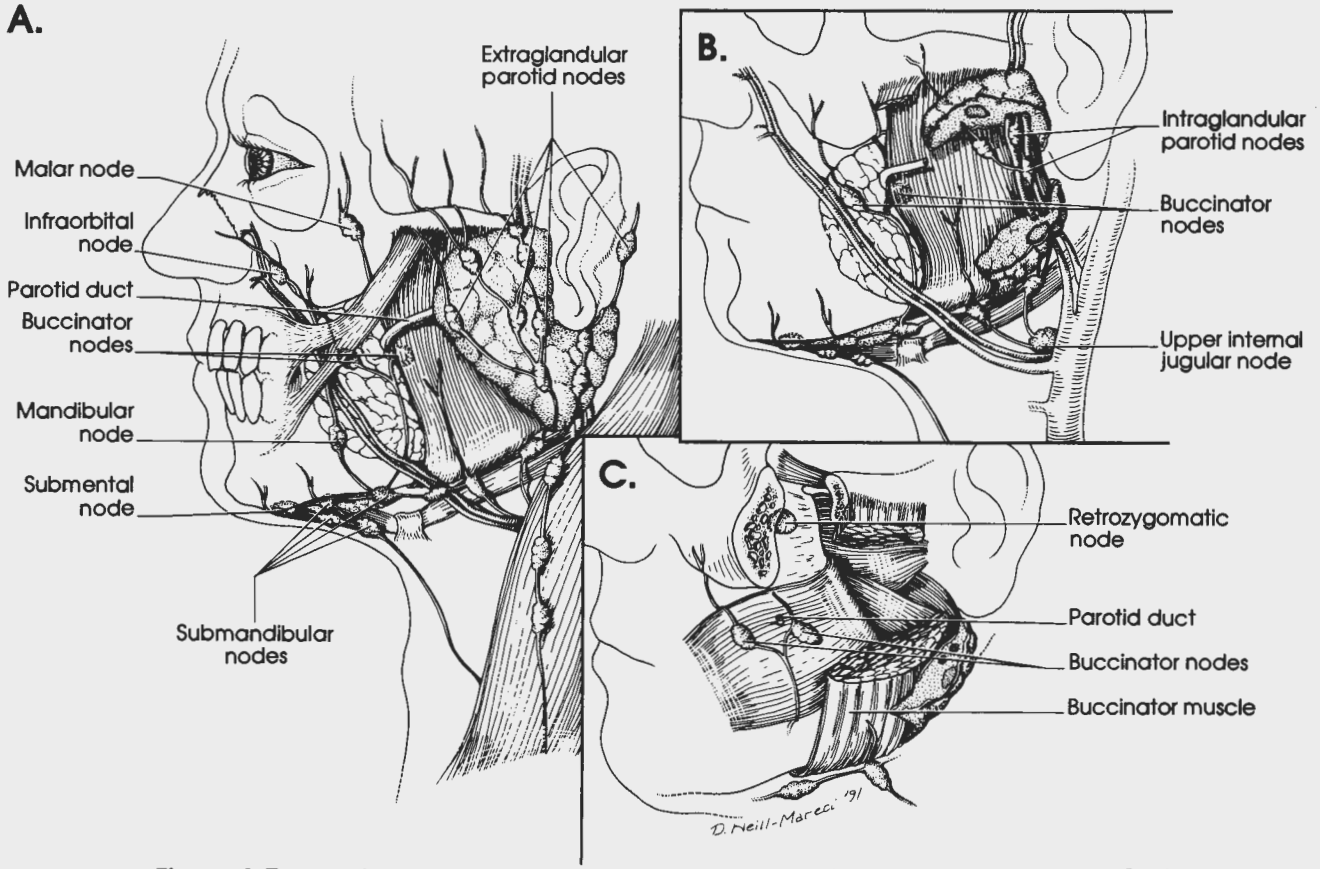

Figure 6-7. Facial and parotid nodes as seen on increasingly deeper dissections. (*A*) Superficial facial nodes (malar, infraorbital, buccinator, mandibular). Their main drainage pathway is to the submandibular group. (*B*) The buccinator nodes are the deepest of the facial group. Intraglandular parotid nodes typically lie within the parenchyma of the gland, just under the capsule of the gland and along the course of the retromandibular vein within the gland. (*C*) A previously unrecognized node is shown, lying in the fat pad of the infratemporal fossa just behind the body of the zygoma.

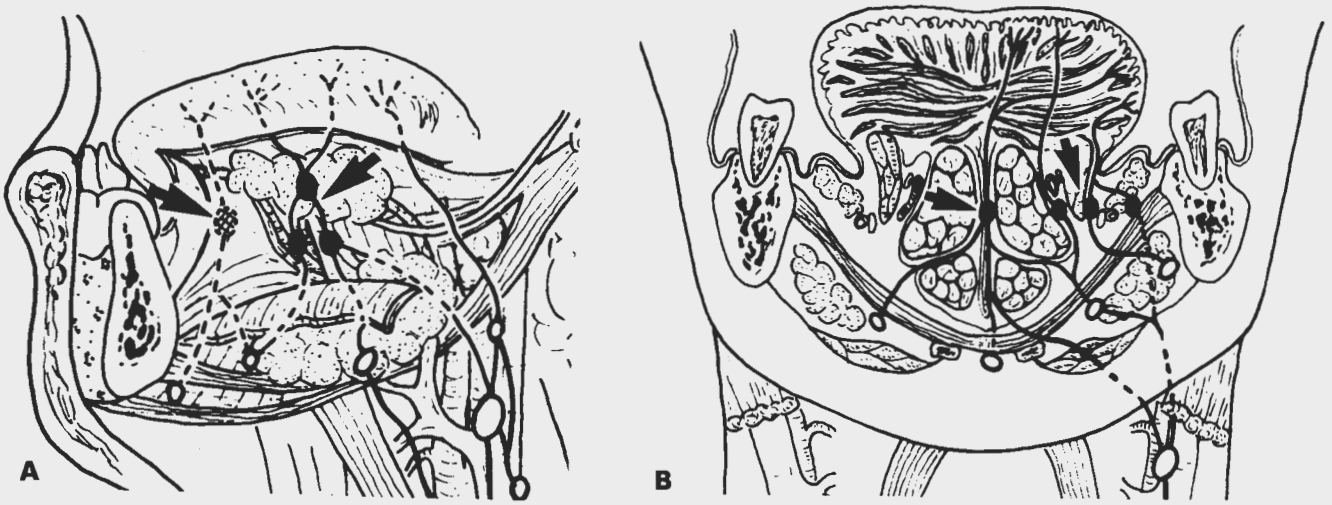

Figure 6-8. Schematic representation of the tongue lymphatics, the lingual lymph nodes (*arrows*), and connections with the cervical lymph nodes. (*A*) Lateral view. (*B*) Frontal view. (Ozeki S, Tashiro H, Okamoto M, Matsushima T. Metastasis to the lingual lymph node in carcinoma of the tongue. J Maxillofac Surg 1985;13:277)

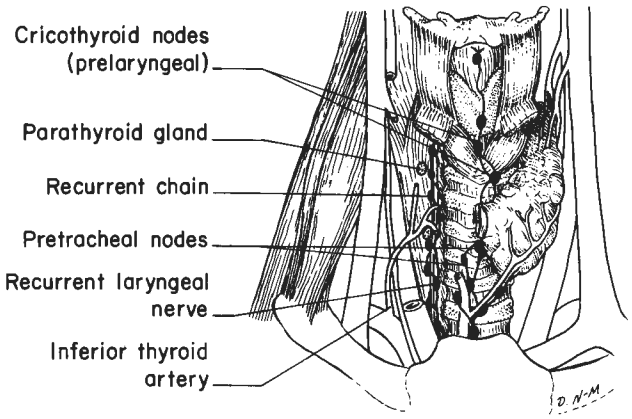

Figure 6-9. Nodes associated with the viscera of the lower neck. Those nodes running near the course of the recurrent laryngeal nerve are usually referred to as tracheoesophageal groove or lateral paratracheal nodes. (Mancuso AA, Hanafee WN. Computed tomography and magnetic resonance imaging of the head and neck, ed 2. Baltimore, Williams & Wilkins, 1985:175)

their dissection relatively easy. The lateral paratracheal chain is continuous with the lymph nodes in the upper mediastinum and is important in the spread of cancers of the larynx, hypopharynx, esophagus, and thyroid gland. These nodes are most likely to be involved when tumor involves the subglottis.

Computed Tomography and Magnetic Resonance Imaging of the Normal Lymph Nodes

The normal anatomic relations of the lymph nodes in the head and neck can be studied with computed tomography (CT; Fig. 6-10).[73a]

On contrast-enhanced CT, normal lymph nodes are typically of homogeneous density and have an attenuation value at least 10 to 20 Hounsfield units less than the opacified blood vessels. Their tissue density is slightly greater than that of surrounding muscle. Normal nodes are not enhanced much more than skeletal muscle. In surgical or anatomic specimens, nodes tend to be oval or elliptical, but their shape on axial sections depends on their orientation to the transverse plane: if the long axis is oriented perpendicular to the plane of section, they may appear round; if it parallels the plane of section, they look somewhat oblong. Larger nodes (1 cm) sometimes appear slightly inhomogeneous. Focal fat deposits may create eccentric lucencies at the hilum of normal-sized nodes or within the gland parenchyma (Fig. 6-11). Accurate measurement of attenuation in the fatty foci may prove difficult because of their small size; however, their density is identical to that of surrounding fat, and they should not be mistaken for metastases. Larger nodes may fold on themselves or over adjacent structures such as muscles or small blood vessels, creating the appearance of a lucency within the nodes; this tendency is most common in the subdigastric group of nodes, which may fold around the posterior belly of the digastric muscle.

On plain magnetic resonance imaging (MRI) studies, normal nodes typically are slightly hyperintense compared with muscle on T1-weighted images. On T2-weighted images, normal nodes are much brighter than skeletal muscle and usually isointense to slightly hyperintense compared with fat (see Fig. 6-6*B* and *C*). On fat-suppressed images, the nodes are much brighter than muscle and about equivalent to other lymphoid tissue. The latter tendency depends on the field strength and technique. On MRI, the internal morphology of normal nodes is homogeneous, even on high-resolution images. On contrast-enhanced MRI, as with CT, little change is visible in normal cervical nodes.

A stated advantage of MRI in evaluating cervical nodes is that the signal from flowing blood in the carotid artery and jugular vein makes the vessels appear as voids (areas lacking signal) that are therefore easily differentiated from the adjacent lymph nodes. As a rule, these vessels are easily distinguished from nodes and other structures, making contrast enhancement unnecessary; however, some caution is needed in this regard. Alterations in blood flow, either turbulence or changes in velocity, can increase the signal intensity in these vessels. The flow rate and size of the jugular veins, especially, may vary greatly from side to side, and some variation must be expected. Atherosclerotic disease may affect the appearance of the arteries.

On cross-sectional images, the normal junctional nodes, when seen, are no more than 3 to 5 mm in size. These are seen in the fat deep to the posterior belly of the digastric muscle.

Along the internal jugular chain, there are common variations in nodal size. Nodes anterior to the vein tend to be larger than those posterolateral to the vein in the upper neck. In the mid and lower neck, the reverse seems to be true. Although there is a distinct tendency for the nodes in the upper internal jugular group to approach and slightly exceed 1 cm in cross section, this is unusual in the mid to lower internal jugular groups.

The low internal jugular nodes lie anterior to the scalene muscle and are immediately adjacent to the thoracic duct–jugulosubclavian vein junction. One cannot usually identify a normal node anterior to the scalene in most patients on CT or MRI.

The spinal accessory nodes lie in the fat of the posterior triangle on cross-sectional images. In adults, the normal spinal accessory nodes range from 3 to 5 mm in diameter and are easily distinguishable from the surrounding fat. The spinal accessory nodes tend to be larger in the upper neck. In children, the internal jugular, retropharyngeal, and spinal accessory nodes frequently are 1 to 2 cm in size. Size criteria under 2 cm are virtually useless in evaluation of these groups in the pediatric age range (see Fig. 6-6*B* and *C*). This is especially true from birth to about 10 to 12 years of age.

Normal submandibular nodes are almost always visible within the fat surrounding the gland on cross-sectional images (see Fig. 6-10). These nodes tend to be 3 to 10 mm in their largest dimension and oval or elliptical. Size criteria are of limited usefulness in evaluating submandibular nodes because these nodes are commonly enlarged as a result of intraoral inflammatory diseases. On axial images, their longest dimension rather than cross section is sampled, which gives a false impression of size compared to other lymph nodes.

The submental nodes are seen as elliptical or round densities within the fat anterior to the hyoid bone.

The parotid area nodes may be intraglandular or extraglandular (see Fig. 6-7). Normal nodes are highly variable in size (1 to 5 mm), position, and number. When visible, they are usually seen in the pretragal region or posterior to the retromandibular vein (posterior facial vein) near the latter's exit from the tail of the parotid (see Chap. 27).

The lateral retropharyngeal lymph nodes are frequently visible on CT and MRI scans at the C1 and C2 levels (see Fig. 6-6). They tend to be round to somewhat elliptical, 3- to 5-mm, soft-tissue densities situated between the internal carotid artery and along the colli and capitis muscles. In children, these nodes frequently measure 10 to 15 mm in cross-sectional diameter. Those reported to occur at the C3 level are not routinely visible in normal subjects. The medial retropharyngeal nodes are not normally seen on imaging studies.

The paratracheal nodal groups are not usually visible on normal CT and MRI studies, or at least cannot be reliably distinguished from small vessels (see Fig. 6-9).

Facial nodes are small and rarely identified when normal (see Fig. 6-7).

Observations on the Pathophysiology of the Cervical Lymphatics

The risk of lymphatic spread largely depends on the relative density of the capillary lymphatics in any given site and is largely independent of histology. Tumors with "pushing borders" are less likely to develop lymphatic metastases, and true verrucous carcinoma, the ultimate in pushing borders, almost never invades the lymphatic system. The depth of invasion of the primary lesion correlates with the risk of lymph node metastasis just as the depth of malignant melanoma invasion correlates with lymph node metastasis. The risk of lymph node metastasis increases rapidly with depths of 2 to 4 mm, according to various reports.[97,98,123,129] Most sarcomas originate in tissues such as muscle, bone, or cartilage and, therefore, have little opportunity for lymph node involvement. However, they, too, may metastasize by way of the lymphatic system once they involve areas with capillary lymphatics. Even basal cell carcinoma of the skin, which has a low rate of lymphatic spread, may eventually invade the lymphatic system but usually only after multiple recurrences.

Neoplasms mostly show a radial growth pattern. It is unlikely that the lymphatic trunks, which have a transporting function, play a role in local growth and spread of a neoplasm. If the tumor cells that enter the lymphatic system were to sprout random tumor colonies along the course of the transporting vessels, one would expect to see numerous noncontiguous satellite nodules, an uncommon feature in untreated head and neck carcinoma. Likewise, operations that do not remove the intervening lymphatic vessels would not succeed. For example, a discontinuous excision of the tongue with radical neck dissection does not remove the intervening lymphatic vessels, but it is a successful procedure. However, when the lymphatic vessels become obstructed, tumor cells may colonize the vessels.

Injection of the lymphatics of the human larynx before laryngectomy shows two patterns of lymph flow. Injection of the deeper lymphatics reveals a unilateral flow without crossover. Injection of the superficial submucosal lymphatics shows a nondirectional pattern of flow to both sides.[111] It is doubtful that the lymphatic vessels are important in local spread of tumor.

Normal cervical lymphangiograms after a retroauricular injection show a strictly ipsilateral flow without contralateral cervical filling.* A surgical incision that interrupts the jugular vein lymphatic trunks (eg, for biopsy of a lymph node) causes nearly complete ipsilateral obstruction, as do some enlarged lymph nodes with metastatic cancer[36] (Figs. 6-12 and 6-13). Surgical obstruction of the deep lymphatic trunks is permanent, and the trunks do not reunite. Radiation therapy causes partial obstruction secondary to a diminution in the number and size of the lymphatic trunks and lymph nodes, and the degree of obstruction is dose-related. Hyperplastic nodes without cancer can also produce partial lymphatic blockage. Cervical lymphangiograms after radical neck dissection may show remaining lymph nodes, particularly in the junctional area, a potential weak spot in a neck dissection[36] (Fig. 6-14).

When cervical lymphangiography is done after radical neck dissection, a persistent nearly complete ipsilateral obstruction is observed; there is a subcutaneous diversion of the lymph flow anteriorly toward the submandibular area. In some cases, Fisch could demonstrate shunting across the submentum to the contralateral jugular chain lymph nodes[36] (Figs. 6-15 and 6-16). The lymph is thus diverted to the opposite side by the submental route after unilateral neck dissection; there is no obvious shunting toward the posterior neck. An example of abnormal contralateral metastatic spread for a well-lateralized primary tumor of the retromolar trigone 20 years after removal of a submandibular salivary gland is given in Figure 6-17.

After bilateral neck dissection, the lymph is shunted to the dermal lymphatics. The dermal lymphatics do regrow across a surgical scar and eventually provide a lymphatic escape pathway[36] (Fig. 6-18). The lymphatic vessels remaining after neck dissection becomes dilated as a result of the obstruction and the valves become incompetent. Addition of irradiation to the neck after neck dissection further obstructs the lymphatic pathways.

Radiation therapy without radical neck dissection causes a decrease in the number and caliber of the lymph vessels, and the nodes decrease in size[36] (Fig. 6-19). Perilymphatic and perinodal fibrosis may be seen as early as 6 weeks after completion of treatment.[36] Complete lymphatic obstruction such as is seen with neck dissection does not occur within the range of clinically used doses. Irradiation does not immediately seal off the lymphatics, but it certainly produces a partial obstruction. The degree of lymphatic change is dose- and volume-related. After high-dose radiation therapy to both sides of the neck, lymph flow is mostly diverted anteriorly to the submental space (just as with surgical obstruction), and an accumulation of lymph occurs in the submental space, creating an unsightly but painless bag of water, which is referred to as a wattle because it resembles a turkey wattle. This lymphedema gradually disappears in 6 months to 1 year. However, this chronic lymphedema results in a degree of permanent fibrosis.

(text continues on page 89)

* We are indebted to Dr. U. Fisch, a head and neck surgeon at the University of Zurich, who has studied the cervical lymphatics by lymphangiography and reported his data in an excellent monograph, *Lymphography of the Cervical Lymphatic System.*[36]

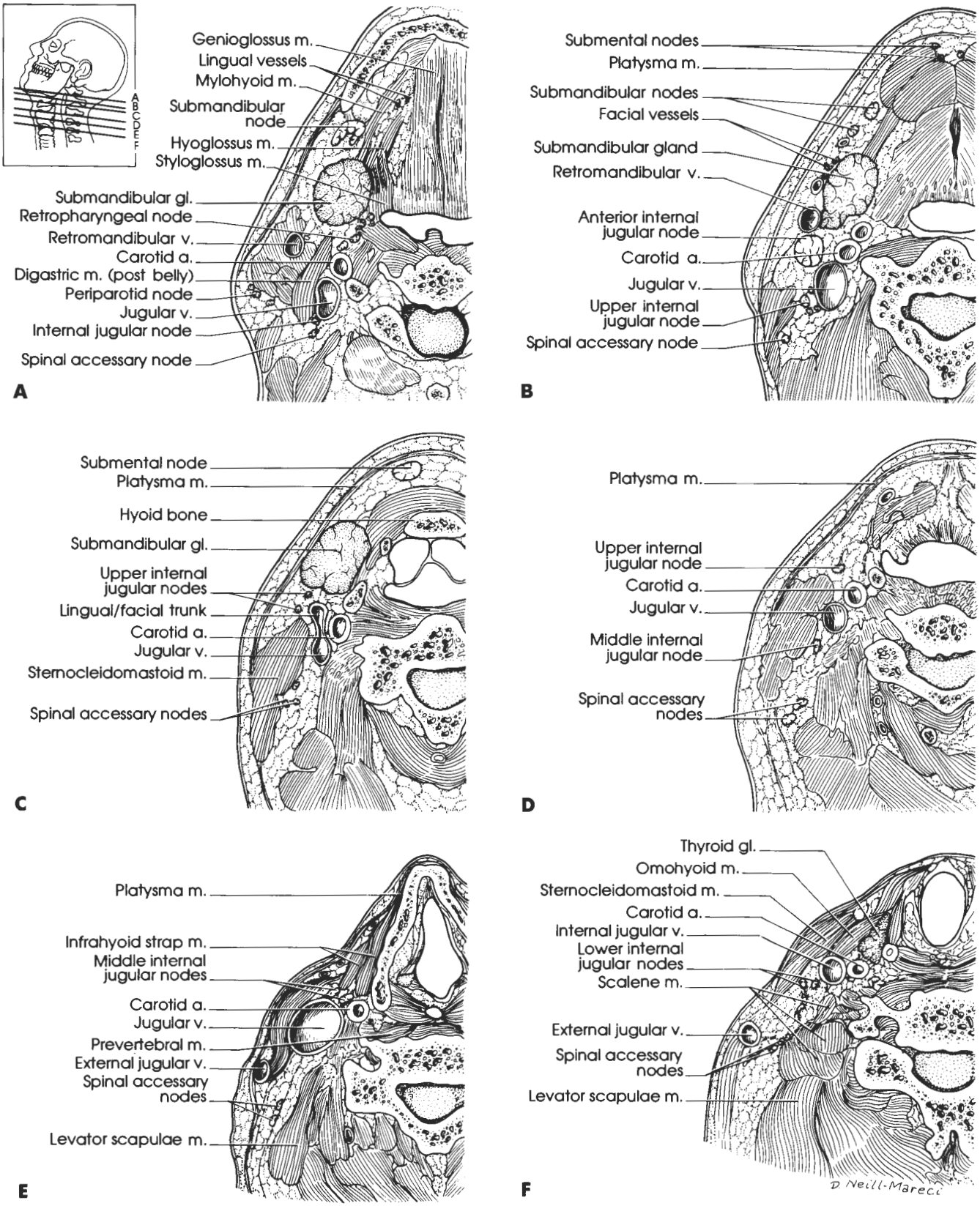

Figure 6-10. Line diagrams and corresponding CT sections demonstrate the positions of the submandibular, submental, internal jugular, and spinal accessory nodes from the level where the posterior belly of the digastric muscle crosses the jugular vein to the level where the omohyoid muscle crosses the jugular vein. (Mancuso AA, Harnsberger HR, Dillon WP. Workbook for MRI and CT of the head and neck, ed 2. Baltimore, Williams & Wilkins, 1989:204–205)

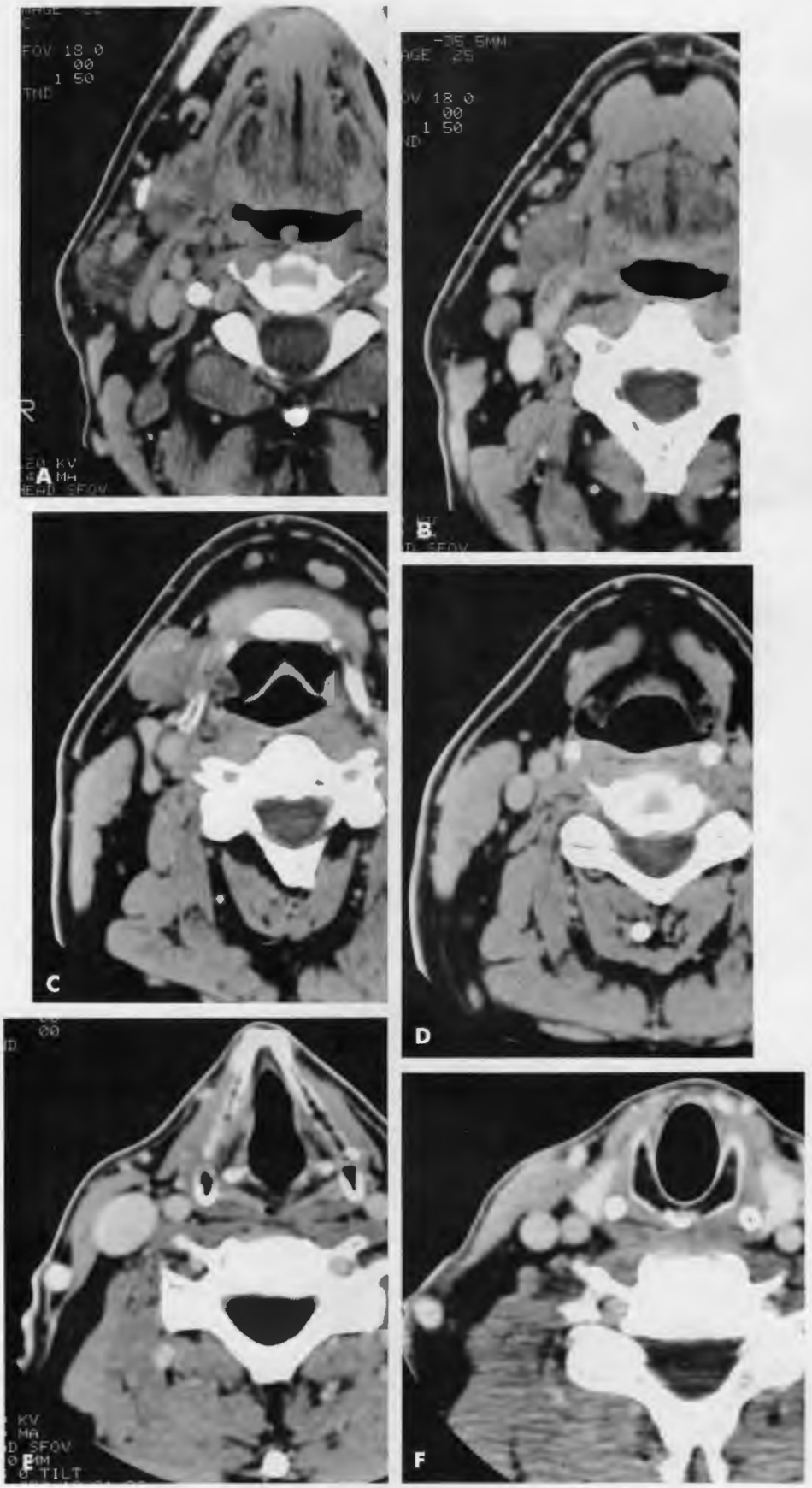

Figure 6-10. (*Continued*)

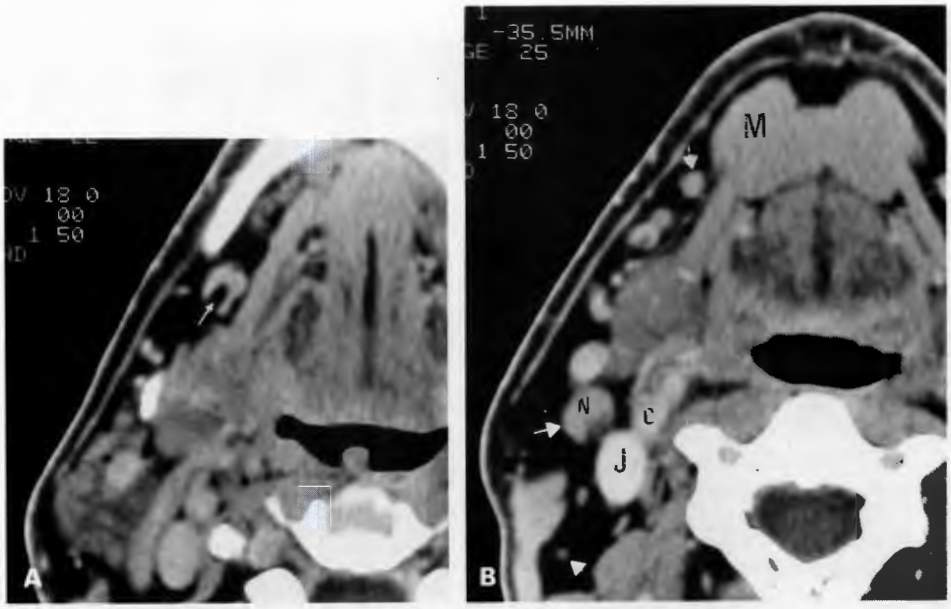

Figure 6-11. Variations in normal nodal architecture. (*A*) A prominent fatty hilum (*arrow*) is seen in a preglandular submandibular lymph node. (*B*) Numerous small lymph nodes are present in the submandibular, upper internal jugular, and spinal accessory groups (*arrows*). These are about the same density as the surrounding muscles (M) but obviously less dense than the enhancing carotid artery (C) and jugular vein (J). The surface of an upper internal jugular lymph node on the right (N) has a small groove where it is either folded over or indented by the posterior belly of the digastric muscle (not seen here but present on the section immediately cephalad to this one).

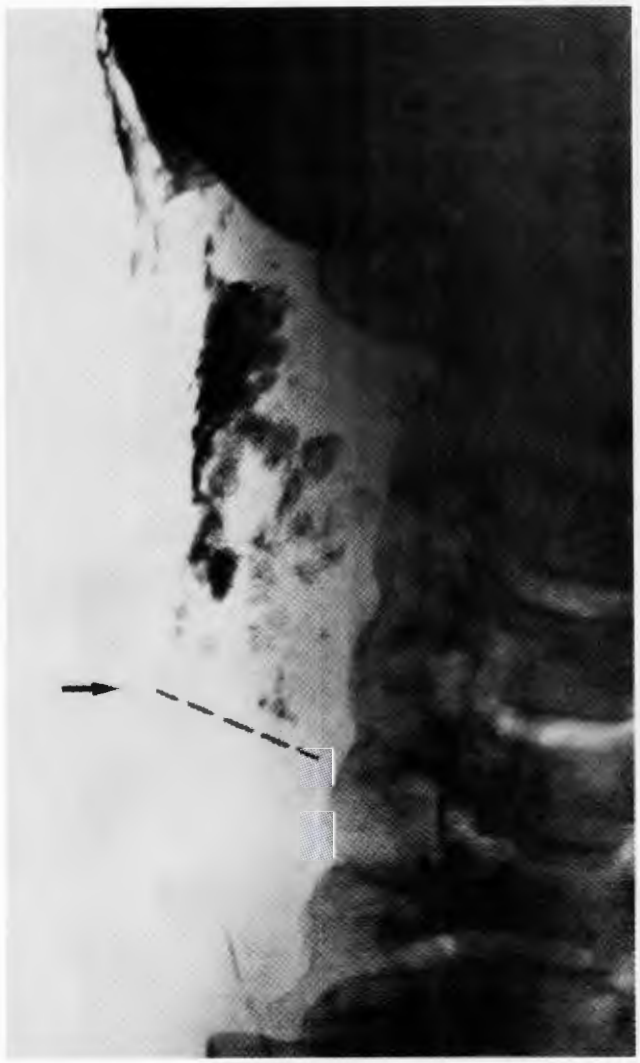

Figure 6-12. Cervical lymphangiogram after incisional biopsy. There is almost complete lymphatic obstruction. (Fisch U. Lymphographische Untersuchungen über das zervikale Lymphsystem [Forschritte der Hals-Nasen-Ohrenheilkunde, vol 14]. Basel, Karger, 1966:127)

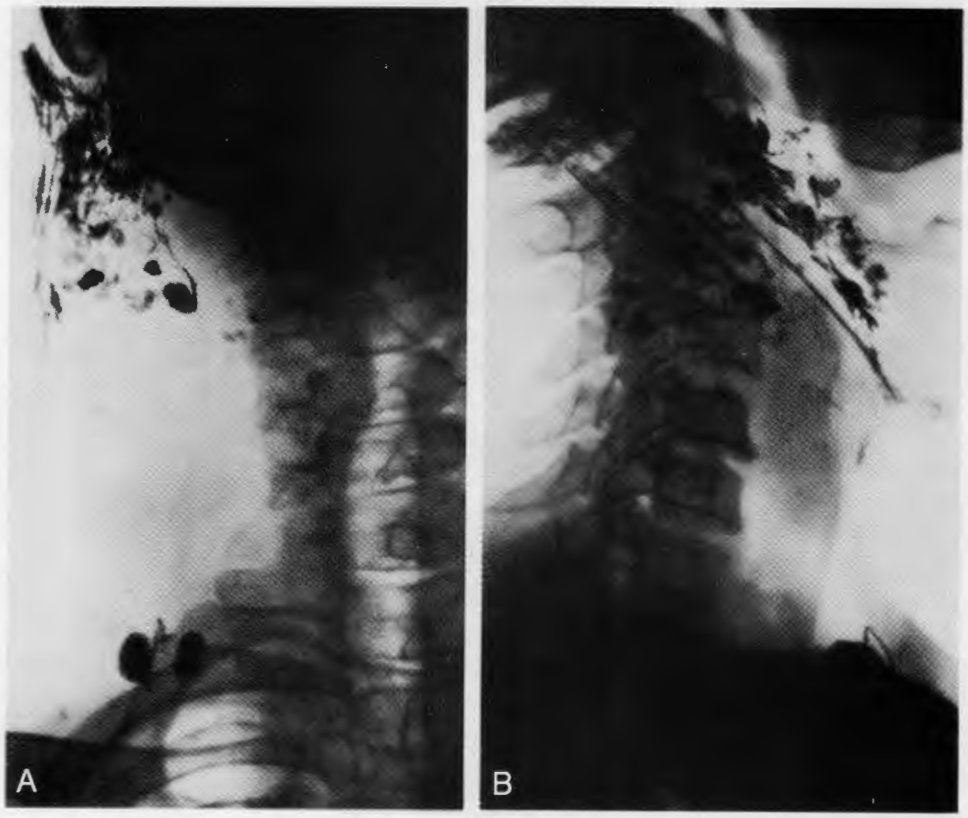

Figure 6-13. Cervical lymphangiogram in patient with carcinoma of the hypopharynx and large right cervical lymph node metastases (late image). Note persistence of contrast medium in lymphatic vessels due to obstruction by tumor in lymph nodes. Two supraclavicular lymph nodes are filled. (*A*) Anteroposterior. (*B*) Lateral. (Fisch U. Lymphographische Untersuchungen über das zervikale Lymphsystem [Forschritte der Hals-Nasen-Ohrenheilkunde, vol 14]. Basel, Karger, 1966:113)

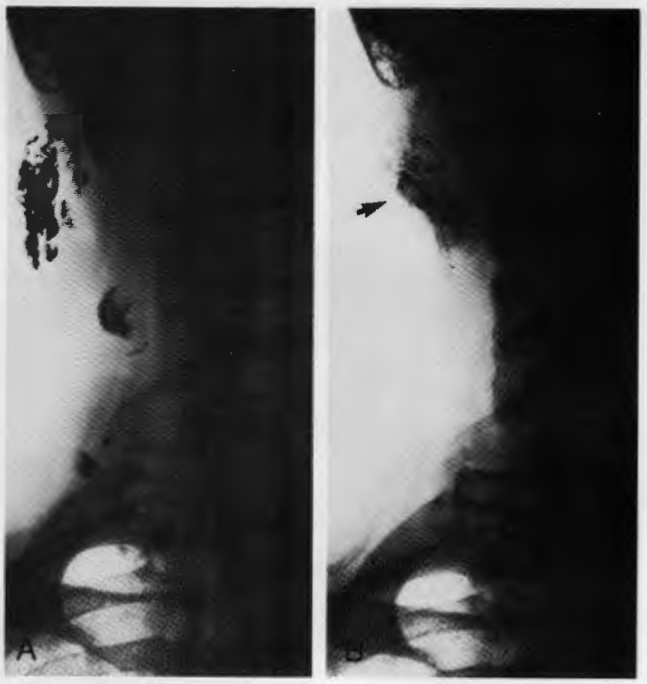

Figure 6-14. (*A*) Preoperative cervical lymphangiogram. (*B*) Postoperative film 2 days after radical neck dissection. Arrow indicates a lymph node suspicious for metastatic carcinoma. Residual metastatic carcinoma was later confirmed by histologic examination. The silhouette of the suction catheter is seen. (Fisch U. Lymphographische Untersuchungen über das zervikale Lymphsystem [Forschritte der Hals-Nasen-Ohrenheilkunde, vol 14]. Basel, Karger, 1966:135)

Figure 6-15. Left cervical lymphangiogram 5 years after radical neck dissection. There is diversion of lymph across the submental space to the contralateral internal jugular chain. Note the low left supraclavicular node lying in the lateral supraclavicular space (*arrow*). (Fisch U. Lymphographische Untersuchungen über das zervikale Lymphsystem [Forschritte der Hals-Nasen-Ohrenheilkunde, vol 14]. Basel, Karger, 1966:142)

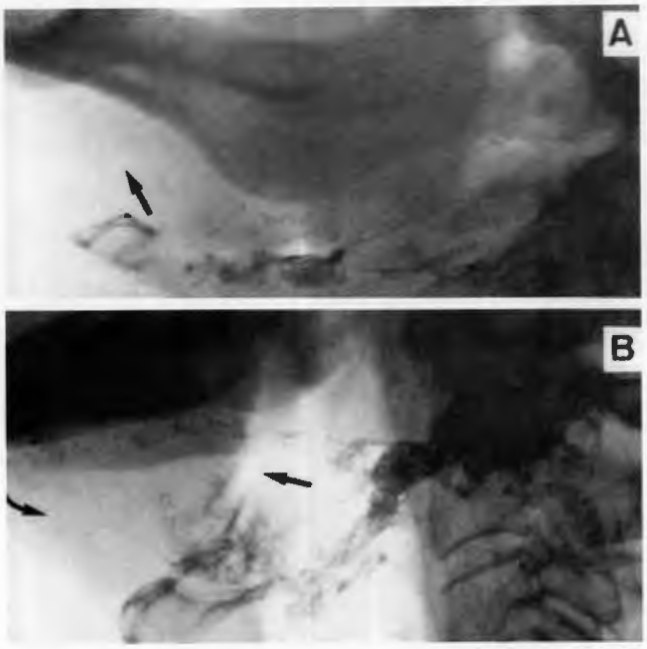

Figure 6-16. (*A*) Cervical lymphangiogram 13 months after radical neck dissection. There is filling of fine lymphatic channels along the mandible, and numerous small lymph nodes can be seen. The arrow points to the submental diversion of the lymph to the contralateral side. (*B*) Left cervical lymphangiogram 5 years after radical neck dissection (same patient as in Fig. 6-18). Arrows point to the submental diversion to the opposite side. (Fisch U. Lymphographische Untersuchungen über das zervikale Lymphsystem [Forschritte der Hals-Nasen-Ohrenheilkunde, vol 14]. Basel, Karger, 1966:140)

Figure 6-17. This patient presented with a T2 squamous cell carcinoma of the left retromolar trigone. Twenty years earlier, he had the left submandibular gland removed because of an inflamnıatory process. A single metastatic lymph node was found and confirmed in the right submental area.

When treating with irradiation, spare as much of the skin and subcutaneous tissues as possible, so as to preserve as much of the dermal lymphatic system as possible and help reduce lymphedema (Fig. 6-20). Preservation of skin lymphatics can be accomplished by shielding of skin or by using high-energy photons. The situation is analogous to that found in the irradiation of extremity sarcomas, where preserving a strip of normal skin and subcutaneous tissues reduces the risk of lymphedema. In the head and neck cancer patient, the skin and subcutaneous tissues of the submentum and anterior midline of the neck are shielded whenever possible. Techniques that unnecessarily flash the skin anteriorly are undesirable. It may require considerable technical effort to shield small strips of skin, but this sparing is often the difference between lymphedema and little or no lymphedema, particularly of the larynx.

Relation of Lymphatics and the Cerebrospinal Fluid

Although most cerebrospinal fluid (CSF) is absorbed by the arachnoid villi and passes mainly into the dural sinuses, there are avenues for CSF to escape directly into the lymphatic system. One of the major avenues is by way of the arachnoid sheaths of the olfactory nerves, which penetrate the cribriform plate and connect with

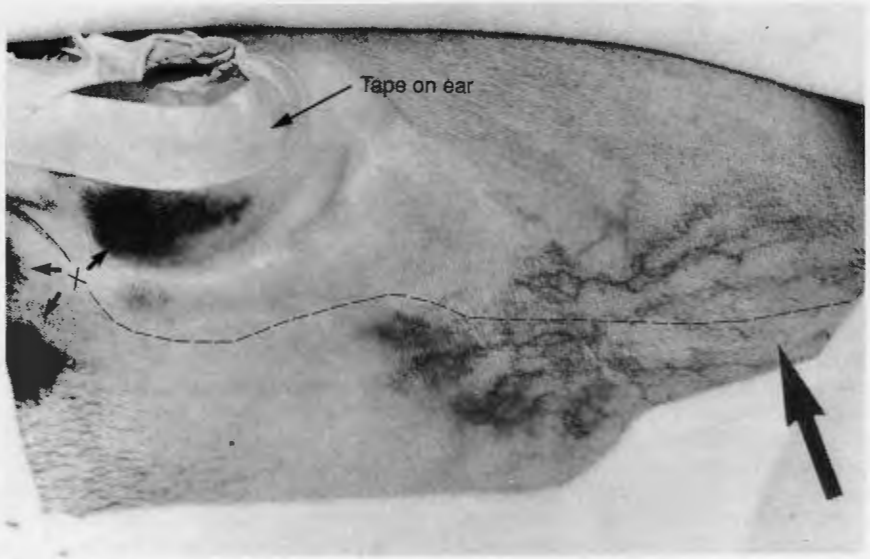

Figure 6-18. Retroauricular injection (x) of patent blue dye 3 years after bilateral radical neck dissection. The dye is picked up by the dermal lymphatics and carried toward the submandibular area. The large arrow pionts to the incision. The dermal lymphatic vessels have regrown across the scar. (Fisch U. Lymphographische Untersuchungen über das zervikale Lymphsystem [Forschritte der Hals-Nasen-Ohrenheilkunde, vol 14]. Basel, Karger, 1966:145)

Figure 6-19. Cervical lymphangiogram 7 months after radiation therapy with 7000 cGy. (*A*) Filling phase. Note fine caliber and decreased number of lymphatic vessels. (*B*) Late phase. Lymph nodes are small and irregularly but densely filled by the contrast medium. The reduced diameter of the vessels causes an increase in intralymphatic pressure, which results in extensive extravasation of contrast medium in the junctional area. (Fisch U. Lymphographische Untersuchungen über das zervikale Lymphsystem [Forschritte der Hals-Nasen-Ohrenheilkunde, vol 14]. Basel, Karger, 1966:162)

capillary lymphatics in the submucosa of the olfactory nasal submucosa. This route of absorption of CSF is probably relatively unimportant, but it can be demonstrated in both humans and animals that blood and other proteins and particles may escape from the anterior cranial fossa through this route. Similar connections have been observed in the spinal cord and brain stem. There also may be a similar connection in the region of the jugular bulb. Földi has shown that complete surgical obstruction of the cervical lymphatics leads to a neurologic syndrome that he called *lymphogenic encephalopathy*, which is characterized by increased CSF pressure, cerebral edema, papilledema, lymphedema of the soft tissues of the head and neck, and lethargy.[43] It seems reasonable that part of the CNS syndrome associated with ligation of the internal jugular veins, especially bilateral ligation, is due not only to venous obstruction but also to the simultaneous lymphatic obstruction.

Figure 6-20. Clothespin applied to anterior midline strip of skin and subcutaneous tissues to increase the amount of tissue shielded. The portal is aligned with skin marks before the clamps are applied.

NECK STAGING

Staging of the neck combines physical examination and contrast-enhanced CT scan or MRI scan. Ultrasound is used in many European countries, but we have little experience with this method.

Physical Examination of the Neck

Reliability of Neck Examination

The reliability of the neck examination depends on the experience and ability of the examiner, the gross anatomy of the individual neck, and whether the neck has been surgically violated or is indurated from prior irradiation. Personal observation over 30 years has made it vividly obvious that there is a wide range of abilities among physicians in the skills of physical diagnosis, and this is particularly true for the neck examination. The neck examination is not difficult, it is just not properly taught in medical schools nor in most residencies. This difference in diagnostic ability surely explains many of the differences in the reported incidence of clinically positive or negative neck examinations.

A fat, short, or muscular neck; a recent surgical procedure such as incisional biopsy, major operation, or tracheostomy; and prior irradiation reduce the ability to palpate enlarged neck nodes. CT is particularly useful in these situations.

Necks judged clinically negative before radiation therapy should be carefully reexamined during the course of therapy, especially during the first 2 weeks. Patients with lymph nodes that were not previously palpable and were negative on CT may sometimes develop

clinically positive lymph nodes; the mechanism is probably tumor necrosis and hemorrhage into tiny involved nodes. Likewise, palpable adenopathy may show sudden enlargement after the first few radiation treatments.

Technique for Physical Examination

At least 3 to 5 minutes is needed to perform a thorough neck examination. It is important to repeat the examination at every opportunity and even more important to compare findings among several examiners. Detailed drawings complement the written report.

The preferred position is with the patient sitting and the examiner standing behind. Because many examination chairs have a head rest or cannot be lowered sufficiently, it is often necessary to move the patient to a regular chair or stool so that the patient's neck is opposite the examiner's waistline. It is common to observe neck examinations being done by patting the neck with the fingers (the "after-shave" method); this method is not acceptable (Fig. 6-21).

We prefer to start at the sternal notch and work upward. The retrosternal space, the space that extends into the upper mediastinum, and the tissues behind the insertion of the sternocleidomastoid muscle to the clavicle are explored with the index finger (Fig. 6-22). Normally, nothing should be felt except the anterior wall of the trachea. Clinically positive lymph nodes are frequently found in this area, but only the top or side of the lymph node may be felt. The enlarged nodes are usually located

Figure 6-22. Neck examination: Exploration of suprasternal space.

Figure 6-21. Neck examination: **IMPROPER** technique.

1 to 2 cm from the midline. Metastatic cancer in lymph nodes from the throat, abdomen, and breast as well as lymphomas and miscellaneous other masses may be felt in this area. This is one of the most commonly missed physical findings. The differential diagnosis of a mass in this area includes thyroid mass, aneurysm of a major vessel, and mediastinal mass.

When the examination of the internal jugular chain is begun and the neck is grasped, the patient instinctively extends the neck, thereby tensing the sternocleidomastoid muscle (Fig. 6-23). Because the internal jugular chain lymph nodes lie deep to the sternocleidomastoid, it is essential to have the neck muscles relaxed. Therefore, one hand is placed on the patient's occiput to flex the head forward and slightly to the side being examined (Fig. 6-24). If the patient is tense, gentle rocking of the head along with gentle massage of the neck often provides the relaxation necessary. The right neck is examined with the right hand, and the left neck is examined with the left hand. Most of the internal jugular chain lymph nodes lie deep to the sternocleidomastoid muscle. The thumb and index finger form a C around the sternocleidomastoid muscle (Figs. 6-25 and 6-26). The tips of the examining thumb and fingers nearly meet on most patients. As one proceeds up the jugular chain, the thumb and index finger are in constant motion, using a wiggle-waggle maneuver. Enlarged lymph nodes can be felt to pop between the examining fingers. Positive lymph nodes in the lower jugular area are often small, mobile, and deep, and only slow, careful, gentle, repeated examinations find them. Most clinically positive lymph nodes are found in the upper jugular chain. The carotid artery and carotid bulb are identified by the pul-

Figure 6-23. Neck examination: Neck is extended to contralateal side; sternocleidomastoid muscle is tensed.

Figure 6-24. Neck examination: Hand on occiput is used to control the head. The neck is flexed forward and to the side that is being examined.

sation in the vessel. The pressoreceptors in the carotid bulb respond to external pressure as well as internal vascular pressure. Stimulation produces a drop in blood pressure and slowing of the pulse. The response is more sensitive in older patients. Patients may develop slight faintness or sudden syncope and collapse. Palpation of the bulb must be gentle and *must not be done simultaneously on both sides*. Palpation of the carotid artery may rarely cause an atheromatous plaque to be splintered from the artery. In one such instance, the patient noted a sudden change in vision in the ipsilateral eye during neck examination. Eye examination confirmed that a branch of a retinal vessel had been occluded, presumably from a small thrombotic plaque entering the ophthalmic artery.

The subdigastric lymph node (tonsillar node) is the largest normal node in the neck and can be identified in many people. Although an involved subdigastric lymph node is sometimes felt deep to the sternocleidomastoid muscle, the more common situation is that the node lies anterior to the sternocleidomastoid muscle just below the angle of the mandible and is felt by gently rolling the index finger through the tissues in this area. A metastatic lymph node mass may be deep in the neck in the subdigastric area, and only the external surface of the mass may be felt. The junctional lymph nodes are difficult to palpate, particularly in men, because the well-developed sternocleidomastoid muscle and the posterior belly of the digastric muscle intervene, and the attachment of the muscles to the mastoid tip restricts the examining fingers.

Figure 6-25. Neck examination: The thumb and index finger form a C to palpate beneath the sternocleidomastoid muscle.

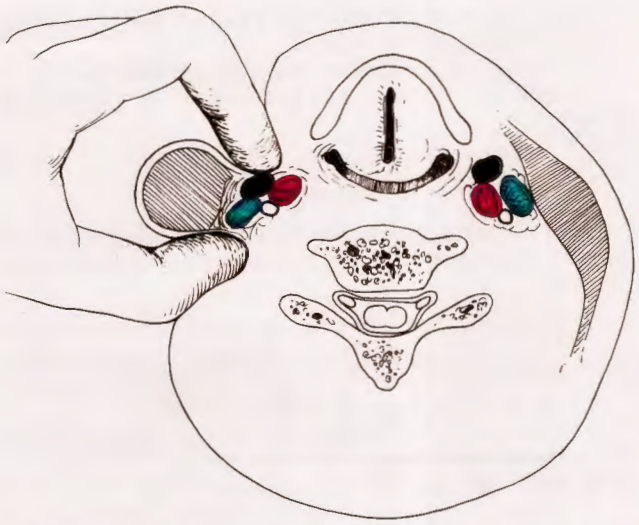

Figure 6-26. Diagram of technique shown in Figure 6-25.

There are a number of normal structures that may be confused with a jugular chain lymph node. The lateral tip of the transverse process of C1 or C2 may feel like a 1- to 2-cm lymph node. The transverse process is especially conspicuous in patients with long, thin necks. The tail of the parotid gland becomes firm, discrete, and globular in older, obese patients, especially men, and resembles a lymph node. This mass lies just below the ear lobe, between the mandible and the tip of the mastoid. The palpable parotid tails are usually symmetrical, which gives a clue to their identity; clinically positive nodes in the tail of the parotid are unusual except in parotid malignancies, skin cancers, lymphomas, or leukemias. The carotid bifurcation (carotid bulb) may be prominent in older people and feel like a subdigastric lymph node. Gentle palpation to determine pulsation of the vessel helps to distinguish the vessel from the node. The differential diagnosis is especially difficult when a 1.5- to 2-cm node is closely approximated to the carotid bifurcation. Localized atheromatous plaques along the carotid produce a localized fusiform enlargement that may be confused with a small lymph node. CT scan is useful in these cases.

Both the submandibular and submental nodes are examined bimanually with one index finger in the floor of the mouth (Fig. 6-27). The submandibular lymph nodes lie along the body of the mandible. The submandibular gland may be small and firm and tucked up underneath the mandible, especially in young patients. The patient should be asked to close the mouth slightly during the examination (but not bite the examiner's finger) because if the the mouth is opened forcefully, the floor of mouth musculature is tensed and adequate examination is not possible. Frequently, the gland lies in the neck just below the mandible, especially in older people. If the submandibular duct is obstructed by tumor, the gland may be enlarged, firm, tender, and immobile. Several lymph nodes lie in juxtaposition to the submandibular gland, and small lymph nodes are located inside the capsule of the gland. It is often impossible to distinguish between an enlarged submandibular gland and an enlarged lymph node. A submandibular gland may be enlarged because of tumor, duct obstruction, inflammation, or radiation effect. If the mass is tender or painful, it suggests inflammation rather than cancer, but the finding is not reliable. Needle biopsy is helpful if positive for cancer. CT is a reliable means of distinguishing cancer in submandibular lymph nodes from submandibular gland enlargement due to inflammation or obstruction. Removal of the submandibular gland may be necessary for diagnosis. A common error in evaluating the neck has been in underestimating the findings in a submandibular mass until the diagnosis of metastatic cancer was all too obvious and the disease was unmanageable. An enlarged submandibular mass is better managed by action than by observation.

The submental lymph nodes lie in the midline between the anterior bellies of the digastric muscles. The most commonly involved submental lymph node lies just anterior to the hyoid; rarely, a node is found to be positive just behind the symphysis of the mandible.

Examination of the spinal accessory and supraclavicular lymph nodes requires only light, gentle palpation of the neck. Preauricular lymph node examination is often overlooked. These nodes lie just anterior to the pinna and may be very small when first involved by tumor. Examination of the superficial mastoid, occipital, facial, and Delphian lymph nodes completes the examination.

Imaging of the Regional Lymph Nodes for Metastatic Disease

Imaging of the regional lymph nodes should always be included as part of the evaluation of an upper aerodigestive tract primary tumor. CT and MRI will remain the imaging examinations of choice for staging cervical

Figure 6-27. Neck examination: Bimanual palpation of submandibular and submental lymph nodes and submandibular gland.

nodes for the foreseeable future. Ultrasound is too operator-dependent and limited in scope to have a primary role. CT remains the primary method for staging cervical lymph node metastases at the University of Florida.[73,73a] MRI plays an adjunctive role mainly in the evaluation of the extent of extranodal spread (especially to the carotid) when CT is indefinite. If MRI is to be used for imaging of the primary site, MRI is also used for the neck. Our practice is to use MRI first only for nasopharynx lesions and to use CT first for other sites.

Basically, imaging can do two things: first, demonstrate positive nodes undetectable by clinical examination and, second, show the presence and extent of extranodal spread.

With good quality CT images, the following can occur:

- A 5% to 10% incidence of upstaging clinically N0 necks to N positive (Fig. 6-28)[73a]
- A significant incidence of upstaging clinically positive necks, often on the basis of finding bilateral disease or additional small positive nodes (see Fig. 6-28)
- Occasional downstaging from clinically positive neck to N0 in patients who are difficult to examine or have an equivocal neck examination (Fig. 6-29). Downstaging most often occurs when the CT scan changes the clinical diagnosis of metastatic cancer in a submandibular lymph node to benign enlargement of the submandibular salivary gland.
- Detection of capsular penetration and perinodal spread of tumor in nodes as small as 8 to 10 mm (Fig. 6-30).

Indications for CT Imaging

The following are indications for CT imaging of the neck in patients with known or suspected head and neck cancer:

1. Evaluation of the primary tumor is extended to include the neck. This is the most common indication and can be done at no additional charge in about 10 minutes of added scan time.
2. Determination of the extent of neck disease even if the primary tumor does not require imaging
3. Aid in the differential diagnosis in patients with a neck mass and no obvious primary cancer (Fig. 6-31)
4. CT-guided needle biopsy (see Chap. 4)
5. Evaluation for recurrence in the neck
6. Examination of areas not readily accessible to physical examination, including the following:

   The *retropharyngeal nodes* can be evaluated in detail with CT or MRI, augmented by imaging-

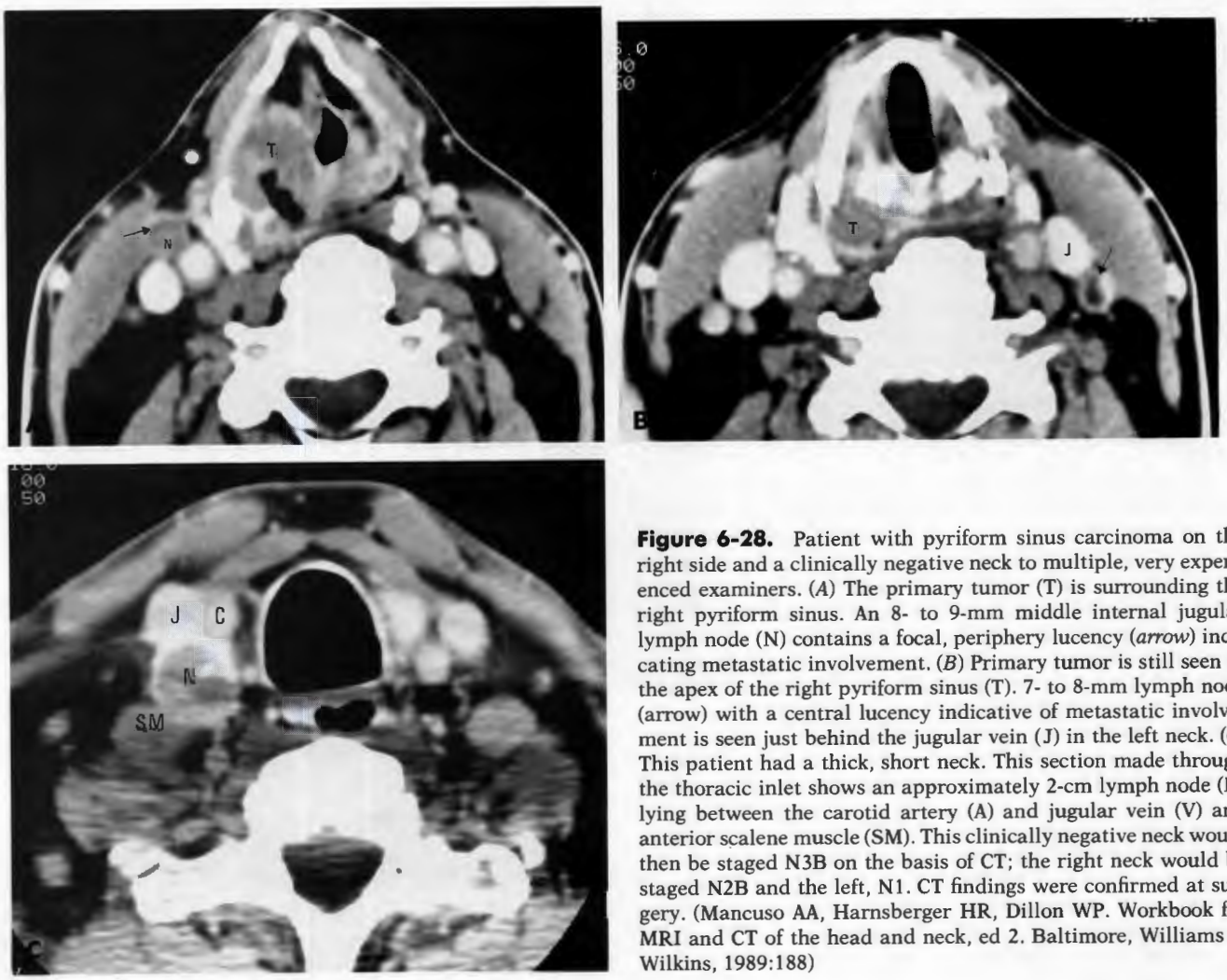

Figure 6-28. Patient with pyriform sinus carcinoma on the right side and a clinically negative neck to multiple, very experienced examiners. (*A*) The primary tumor (T) is surrounding the right pyriform sinus. An 8- to 9-mm middle internal jugular lymph node (N) contains a focal, periphery lucency (*arrow*) indicating metastatic involvement. (*B*) Primary tumor is still seen at the apex of the right pyriform sinus (T). 7- to 8-mm lymph node (arrow) with a central lucency indicative of metastatic involvement is seen just behind the jugular vein (J) in the left neck. (*C*) This patient had a thick, short neck. This section made through the thoracic inlet shows an approximately 2-cm lymph node (N) lying between the carotid artery (A) and jugular vein (V) and anterior scalene muscle (SM). This clinically negative neck would then be staged N3B on the basis of CT; the right neck would be staged N2B and the left, N1. CT findings were confirmed at surgery. (Mancuso AA, Harnsberger HR, Dillon WP. Workbook for MRI and CT of the head and neck, ed 2. Baltimore, Williams & Wilkins, 1989:188)

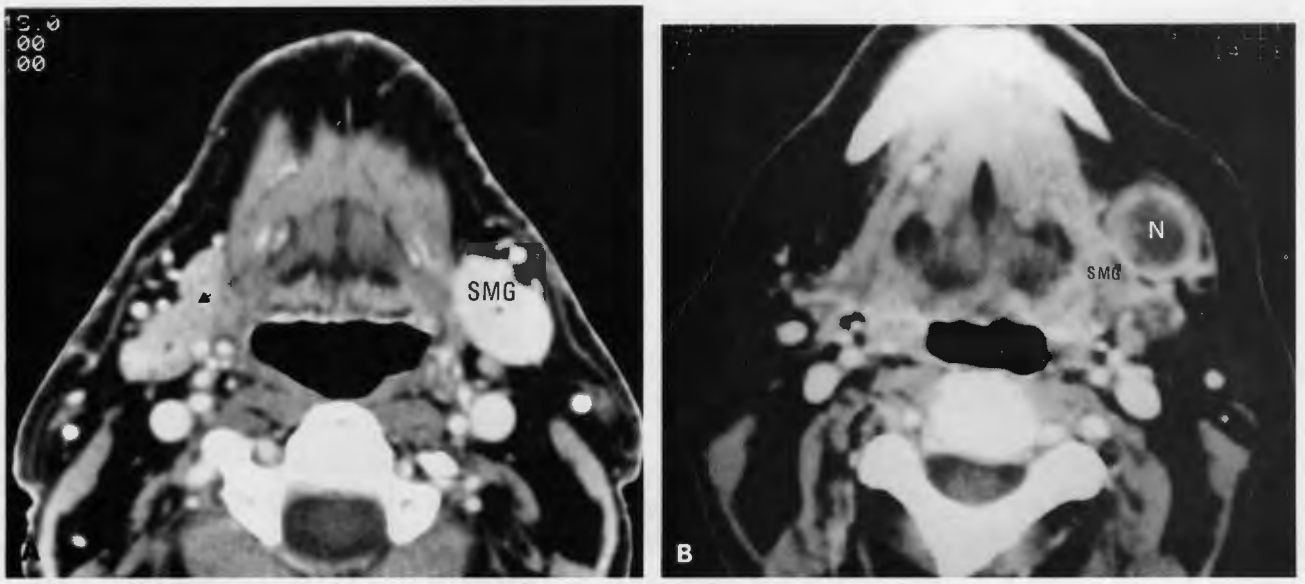

Figure 6-29. CT scans from two patients with carcinoma involving the oral cavity. Each had a palpable mass in the left submandibular gland region believed to be due to metastatic disease to submandibular lymph nodes. (*A*) The palpable mass is in reality due to an enlarged submandibular gland (SMG). The abnormal gland is obviously rounder and more enhanced than its normal counterpart on the right side (*arrow*). (*B*) A metastatic lymph node (N) is the source of the palpable mass in the left submandibular region. It can be seen as separate from the submandibular gland (SMG).

directed percutaneous biopsy when necessary. In patients with nasopharyngeal cancers, the retropharyngeal nodes are almost always enlarged and frequently show evidence of focal metastatic disease but usually do not show evidence of capsular penetration (see Chap. 23).

The *junctional nodes* extend above the posterior belly of the digastric, making detection by physical examination difficult. Enlarged junctional nodes are frequently associated with diffuse fullness and bulging of the sternocleidomastoid muscle behind the angle of the mandible. Cranial nerves IX through XII and the cervical sympathetics lie just medial to these lymph nodes and are occasionally involved secondarily by tumor. Involvement of these nodes can alter the decision to preserve the spinal accessory nerve, especially if there is evidence of capsular penetration (Fig. 6-32).

The *lateral paratracheal nodes* are virtually never palpable even when enlarged. When low neck or paratracheal nodes are positive, the CT examination should be extended to the mediastinal nodes. The CT examination may be extended to include the entire chest and liver because of the high risk of distant metastases. These nodes are most often involved in patients with thyroid cancer (Fig. 6-33).

The pathologically involved *retrozygomatic and facial nodes* are shown in Figure 6-34, and abnormal *lingual nodes* are illustrated in Figure 6-35.

Imaging Criteria of Metastatic Disease in Lymph Nodes

The diagnosis of metastatic squamous cell carcinoma in lymph nodes depends on size, focal parenchymal defects (including central necrosis), rim enhancement, and extranodal extension. By themselves, none of these criteria is specific for metastatic cancer. The lack of specificity is usually a moot issue because the patients have known cancer. It is more of a problem in patients with neck masses of uncertain etiology (see Chap. 15).

SIZE. The division between normal and probable metastatic nodes is arbitrarily taken at 1.5 cm for the jugulodigastric nodes. A diameter of 1 cm is used as the criterion for positivity for the remaining neck lymph nodes. For example, in adults, 1-cm nodes in the parotid, retropharyngeal, or tracheoesophageal groove region would be two to three times the size of those normally found in the general population.

PARENCHYMAL DEFECTS AND CENTRAL NECROSIS. Squamous cell carcinoma has the distinct tendency to become necrotic in lymph nodes, sometimes before the metastatic focus has grown to 1 cm. For this reason, a low-attenuation focus in a normal-sized node is considered to be evidence of metastatic involvement (see Figs. 6-28 and 6-30). Such foci are routinely visible in 5- to 10-mm nodes on CT studies using the techniques outlined in Chapter 4. Once normal anatomy or artifact has been excluded as the origin of the focal abnormality within a node, the presence of a focal defect in a node becomes a reliable criterion for positivity. The presence of a focal defect avoids the ambiguity of size (see Fig. 6-29). CT is much more reliable than MRI for detecting focal metastatic deposits. Both seem equivalent at establishing the size of nodes. Necrosis is not specific for carcinoma and may be seen in suppurative nodes, granulomatous disease (tuberculosis, fungal infection), lymphoma (usually in human immunodeficiency virus [HIV]-positive patients), adenocarcinoma, and melanoma (see Fig. 6-31).

RIM ENHANCEMENT. Rim enhancement is a common finding in metastatic nodes on contrast-en-

(*text continues on page 98*)

Figure 6-30. Three different patients are shown in parts *A* through *E*. In all, the neck was clinically positive, and the nodal masses were freely movable. (*A*) Multiple nodes are present in the left neck. They contain subtle low-density foci strongly suggestive of metastatic involvement. At some points, their margins are slightly indistinct, suggestive of early capsular penetration. The overlying platysma is slightly thickened (arrow), an adjunctive sign of capsular penetration. (*B*) A lower section in the same patient as in *A* shows that the platysma of the left and other deep fasciae are thickened (*arrowheads*). Contrast enhancement is seen between the node capsule (N) and the sternocleidomastoid muscle (*arrow*), another adjunctive sign of capsular involvement, penetration, and possible involvement of the investing layer of deep cervical fascia as it overlies the sternocleidomastoid muscle. (*C*) A second patient with a clinically positive node (N) in the right neck. (*D*) A section taken slightly higher in the same patient as in *C* shows that the tissue planes around the branches of the external carotid artery are obliterated on the right side (*arrows*). Compare this to the normal left side where the normal fat spaces around the external carotid branches lie deep to the posterior belly of the digastric muscle (DM). Surgery confirmed encasement of the external carotid branches on the right. (*E*) A third patient with a movable mass in the right neck. Tumor encased the carotid artery (C), even though the mass was movable.

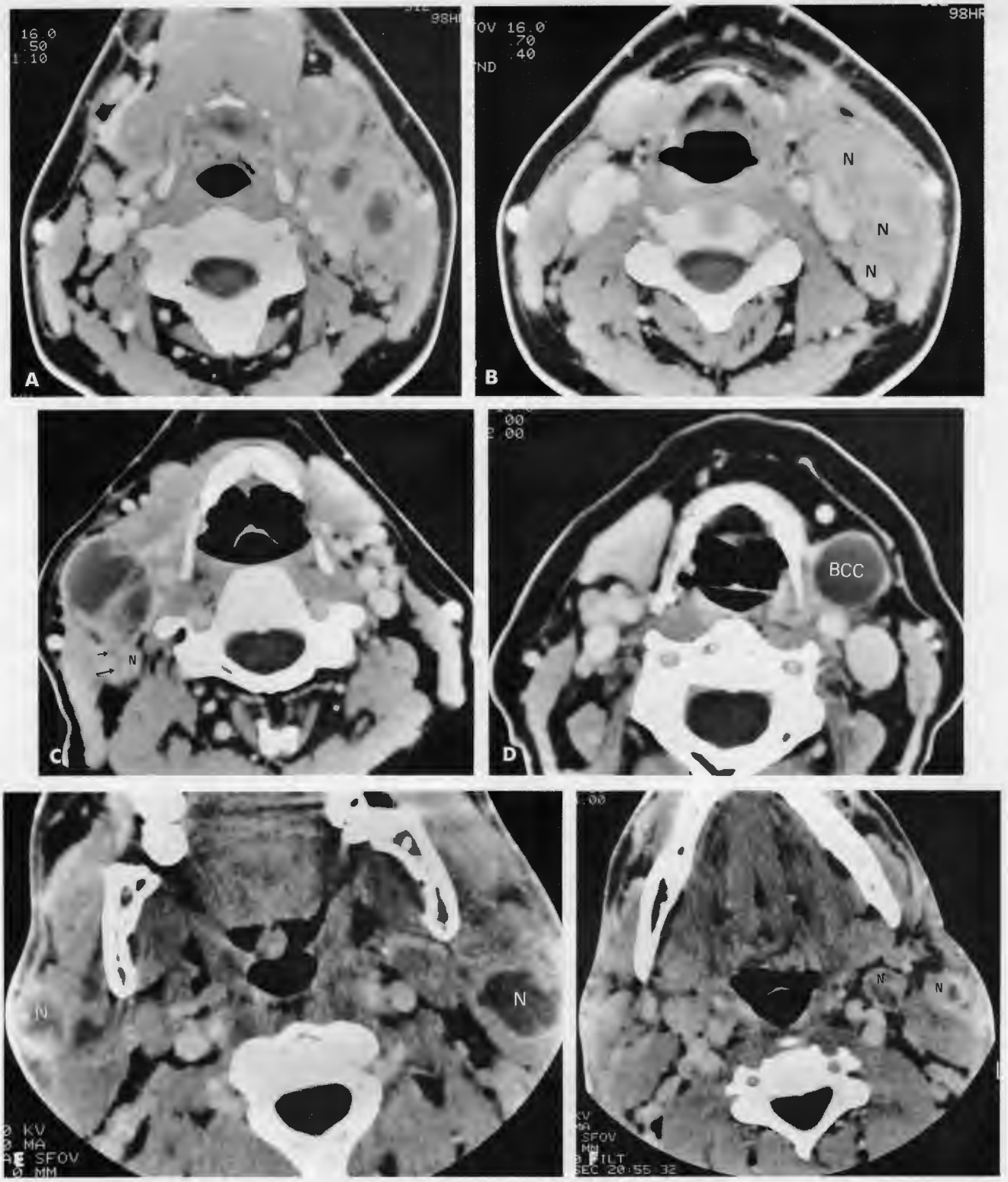

Figure 6-31. CT sections from four different patients with grossly cystic or necrotic neck masses are shown to emphasize the range of lesions that may be demonstrated on CT and MRI studies of the neck. (*A* and *B*) A patient with suppurative adenopathy with a large left-sided conglomerate lymph node mass with obvious areas of necrosis (suppuration) within the nodes. (*B*) The extreme thickening of the platysma and swelling of surrounding soft tissues stronly suggest an inflammatory etiology. The nodes (N) show a morphology typical of reactive adenopathy; this is indistinguishable from a lymphomatous node. (*C*) Patient with carcinoma of the tongue base who had a multiloculated necrotic lymph node mass and a smaller node (N) containing metastatic foci (arrow). Appearance seen here would also be consistent with an infected branchial cleft cyst and related suppurative adenopathy in the proper clinical setting. (*D*) A branchial cleft cyst (BCC) is seen on the left. Occasionally, nodal metastases can have a thin, smooth wall and mimic this appearance. (*E* and *F*) An HIV-positive patient with multiple grossly cystic, rim-enhancing masses within and outside the parotid gland (N). These were due to tuberculous lymphadenitis. In this clinical setting, the lesions within the parotid gland could represent neoplastic or infectious lymph nodes of lymphoepithelial cysts. However, the involvement of the upper neck nodes seen in *F* indicates that this is a process primarily involving lymph nodes, either neoplastic or infectious.

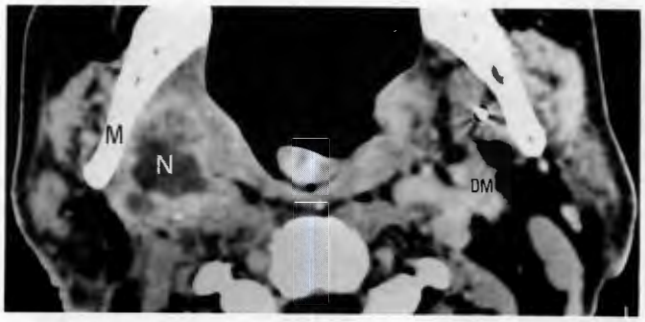

Figure 6-32. This patient had prior surgical and radiation therapy for carcinoma involving the tongue. Clinically, there was no visible or palpable disease, but the patient complained of dysphagia, trimus, and neck pain. Other sections showed extensive recurrent disease at the primary site and within the deep lymph nodes groups. This illustrates an enlarged right junctional lymph node (N). It lies at and above the level of the posterior belly of the digastric (DM on the opposite side) and lies mainly medial and superior to the angle of the mandible (M).

hanced CT scan (see Figs. 6-29 and 6-30). Rim enhancement is nonspecific and can be seen in reactive or infected nodes, lymphoma, or squamous cell carcinoma. Rim enhancement is seen with gadolinium-enhanced MRI and best seen with fat-suppression techniques.

EXTRANODAL SPREAD. Early extranodal spread of tumor is commonly visible on nodes as small as 10 to 15 mm in size, and this correlates with recent pathologic studies that confirm a high incidence of transcapsular spread in nodes of this size (see Fig. 6-30).[100] CT is more sensitive than MRI for detecting early perinodal spread. Refinements in MRI such as fat-suppression techniques and the use of contrast agents may make the two examinations equivalent in the near future. Ultrasound and MRI may be used to determine whether there is carotid extension or spread to the muscles of the floor of the neck. If there is a strong likelihood of carotid extension or encasement and sacrifice of the carotid artery is planned as part of therapy, a preoperative carotid arteriogram with test occlusion can be added to determine the likelihood of a significant neurologic deficit if the carotid is sacrificed. Test balloon occlusion is done with constant monitoring of the patient, in combination with physiologic monitoring of the brain flow with either xenon blood-flow studies or SPECT radionuclide studies.

Adenocarcinomas and malignant melanomas metastatic to lymph nodes produce diagnostic findings similar to squamous cell carcinoma.

Neck Lymph Node Staging System

The 1983 American Joint Committee on Cancer (AJCC) classification system (second edition) is adopted for this book.[3] The N (node) classification for cervical lymph nodes is uniform for all head and neck sites except for the thyroid. The third edition of the AJCC staging manual (1988) included several major changes.[4] The 1988 UICC and AJCC systems are identical. Bilateral cervical metastases were previously classified as N3B and are now N2C. N3 contains only patients with a lymph node greater than 6 cm in diameter. We have continued to use the 1983 neck classification for this edition because most of the world literature uses the 1983 code.

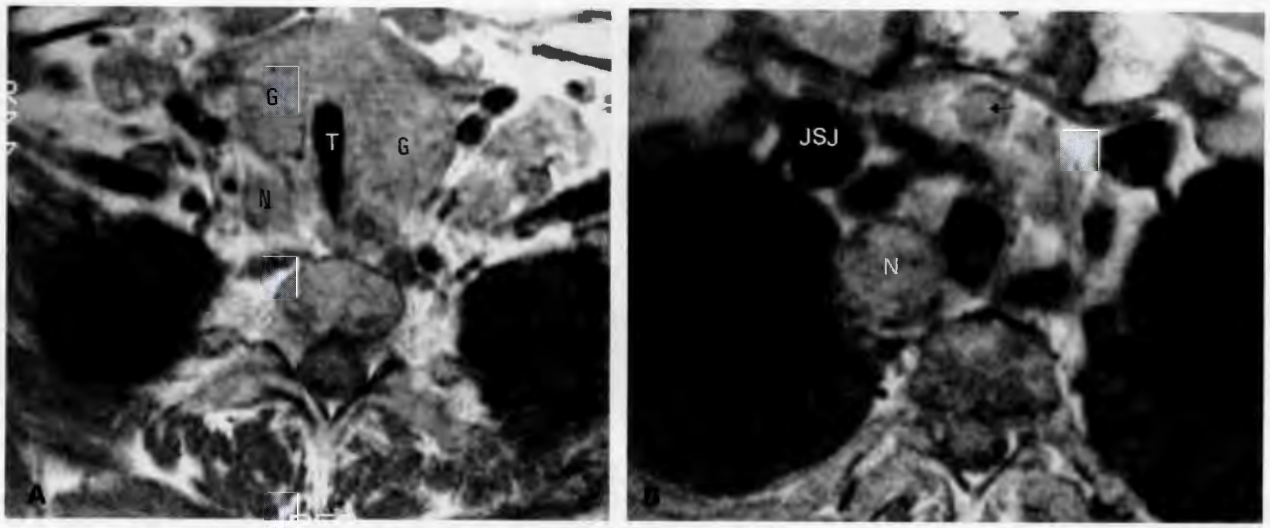

Figure 6-33. (*A*) The lateral paratracheal nodes lie in the tracheoesophageal groove. This patient had diffuse enlargement of the thyroid gland (G) due to papillary thyroid cancer. The tumor also compressed the trachea (T) and spread to a right tracheoesophageal lymph node (N). (*B*) A section through the upper mediastinum showed a second paratracheal lymph node (N); because this node was seen beginning at and for 2 cm below the level of the jugulosubclavian junction (JSJ), it is better considered a mediastinal than a neck node. An additional node was seen in the pretracheal space (arrow).

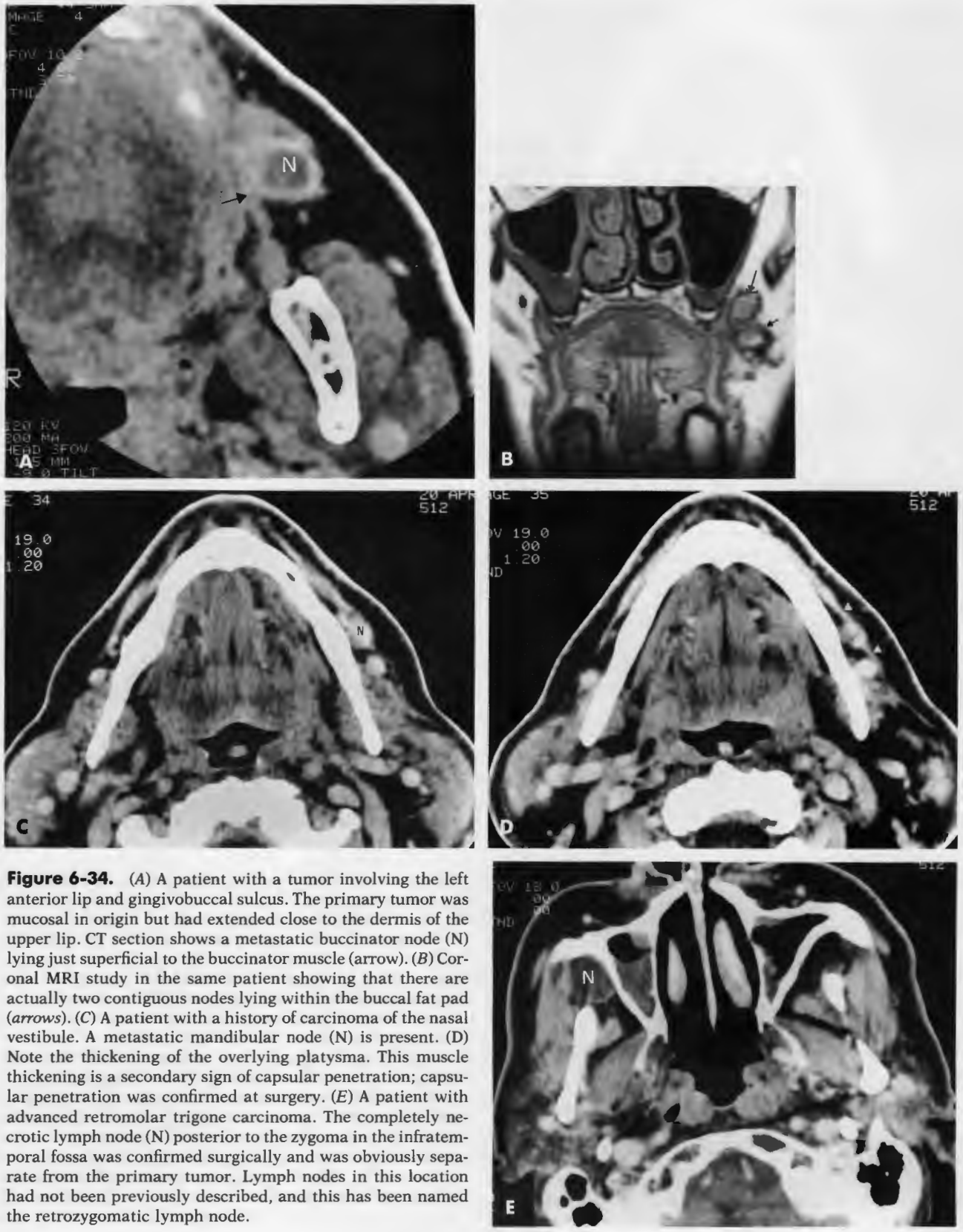

Figure 6-34. (*A*) A patient with a tumor involving the left anterior lip and gingivobuccal sulcus. The primary tumor was mucosal in origin but had extended close to the dermis of the upper lip. CT section shows a metastatic buccinator node (N) lying just superficial to the buccinator muscle (arrow). (*B*) Coronal MRI study in the same patient showing that there are actually two contiguous nodes lying within the buccal fat pad (*arrows*). (*C*) A patient with a history of carcinoma of the nasal vestibule. A metastatic mandibular node (N) is present. (D) Note the thickening of the overlying platysma. This muscle thickening is a secondary sign of capsular penetration; capsular penetration was confirmed at surgery. (*E*) A patient with advanced retromolar trigone carcinoma. The completely necrotic lymph node (N) posterior to the zygoma in the infratemporal fossa was confirmed surgically and was obviously separate from the primary tumor. Lymph nodes in this location had not been previously described, and this has been named the retrozygomatic lymph node.

Figure 6-35. Patient with carcinoma of the oral tongue. An infiltrating mass obliterates the sublingual space in the anterior floor of the mouth (*arrows*). A necrotic lingual lymph node is seen more posteriorly (N). Enlarged upper neck nodes (*arrowheads*) are also present.

NX: Minimum requirements to assess the regional nodes cannot be met
N0: No clinically positive node
N1: Single clinically positive homolateral node 3 cm or less in diameter
N2: Single clinically positive homolateral node more than 3 cm but not more than 6 cm in diameter or multiple clinically positive homolateral nodes, none more than 6 cm in diameter
N2A: Single clinically positive homolateral node more than 3 cm but not more than 6 cm in diameter
N2B: Multiple clinically positive homolateral nodes, none more than 6 cm in diameter
N3: Massive homolateral node, bilateral nodes, or contralateral nodes
N3A: Clinically positive homolateral nodes, one more than 6 cm in diameter
N3B: Bilateral clinically positive nodes (in this situation, each side of the neck should be staged separately; ie, N3B: right, N2A: left, N1)
N3C: Contralateral clinically positive nodes only

The AJCC neck staging system is easy to apply. The concept of whether a node is fixed has been discarded, because there is too much disagreement regarding what is or is not fixed. However, clinical observation of fixation is predictive of outcome in review of our own cases.

The N3C stage has been seen only once in 30 years of observation. It should alert the clinician to look for a second primary lesion or for an anatomic reason, such as previous ipsilateral neck surgery, for rerouting of the lymphatic flow.

NATURAL HISTORY OF NECK LYMPH NODE METASTASIS IN SQUAMOUS CELL CARCINOMA

Tumor emboli traverse lymphatic channels and may establish growth in the subcapsular sinus of a lymph node. This regional metastasis may embolize to an adjacent lymph node, or enter the venous circulation with the possibility of developing distant metastases, usually in the lung. Growth within a lymph node is characterized by gradual replacement of the normal architecture, enlargement of the mass, and frequent invasion into and through the capsule of the lymph node. Microscopic and gross evidence of extracapsular spread may be observed in lymph nodes only partly replaced by tumor. Patchy areas of necrosis develop in the enlarging mass, and a few metastatic masses become cystic with only a thin peripheral lining of squamous cell carcinoma. The cystic metastasis may be mistaken for a branchiogenic cyst or branchiogenic carcinoma.[90]

Risk of Lymph Node Metastasis

The risk of lymph node metastasis may be predicted by the differentiation of the tumor (the more poorly differentiated, the greater the risk), by the depth of penetration of the primary lesion, and by the density of capillary lymphatics at the primary site. Vascular space invasion diagnosed on tissue from the primary site predicts a high rate of metastasis. Lymphatic spread increases with recurrent lesions.

No histology is exempt from lymphatic spread. Minor salivary gland tumors and sarcomas, for example, assume a risk of lymphatic metastasis similar to squamous cell carcinoma for each anatomic site. For instance, a minor salivary gland tumor or sarcoma arising in the nasopharynx would have a relatively high risk for lymphatic metastasis, whereas the same tumors would have a low risk should they arise from the maxillary antrum or hard palate.

A patient may present with a metastatic lymph node and, despite an extensive work-up, have the site of origin remain undetermined. If only the neck is treated, a primary lesion may appear at a later date, but a primary tumor never appears in some cases (see Chap. 15).

The risk of subclinical disease in the lymph nodes in a patient with a clinically negative neck may be determined either by studying the incidence of positive nodes found in elective neck dissection specimens or by counting the number of necks initially normal that become positive when the neck is not treated.

The reported incidence of positive lymph nodes in dissected necks that were clinically negative depends in part on the thoroughness of the pathologic examination.[141] The likelihood of identifying a small metastasis (0.5 to 2 mm in diameter) in the periphery of a lymph node that is 2 to 10 mm in diameter varies with metastasis size, node diameter, and sectioning of the lymph node into halves or quarters. There is little information on serial sectioning of lymph nodes from neck dissection specimens.

The relative risk for cervical metastatic disease from squamous cell carcinomas developing at various sites is outlined in Table 6-2.[82] The relative incidence of clinically positive lymph nodes by anatomic site and T (tu-

TABLE 6-2. Incidence of Lymph Node Metastasis by Site of Primary in Head and Neck Squamous Cell Carcinoma

Site	N+ at Presentation (%)	N0 Clinically N+ Pathologically (%)	N0 → N+ With No Neck Treatment (%)
Floor of mouth	30–59[42,49,58]	21–50[19,52,126]	20–35[5,21,91]
Gingiva	18–52[20,28,42,75]	12–19[19,20]	17[5,20]
Hard palate	13–24[24,33,75]	No data	22[5]
Buccal mucosa	9–31[42,58]	0/10[19]	16[5]
Oral tongue	34–65[42,49,56,58]	25–54[12,28,44,64,127]	38–52[44,56,91,130]
Nasopharynx	86–90[14,69,95]	No data	19–50*[55,96]
Anterior tonsillar pillar or retromolar trigone	39–56[7,59,68]	35[19]	10–15[126]
Soft palate or uvula	37–56[7,59,68]	No data	16–25[68]
Tonsillar fossa	58–76[14,49,59,62,69,95]	No data	22†[118]
Base of the tongue	50–83[59,95,103,109,126]	22–33[19,103]	No data
Pharyngeal walls	50–71[59,95,103,126]	46–66[19,103]	No data
Supraglottic larynx	31–64§[49,126]	16–26[19,103,112]	33[38,112]
Hypopharynx	52–78[28,94,103,126]	38–56[19,103]	No data

* T1 N0 potients only.

† Patients received preoperative irradiation.

§ Golder S, unpublished data, April 1980.

(Modified from Mendenhall WM, Million RR, Cassisi NJ. Elective neck irradiation in squamous cell carcinoma of the head ond neck. Head Neck Surg 1980;3:16)

mor) stage is shown in Table 6-3.[67] The risk for clinically positive nodes and more advanced neck disease increases with the T stage, except for tumors of the nasopharynx and hypopharynx.

Spread Patterns

There is usually an orderly and predictable progression of lymph node involvement, but skips and random involvement may occur. Prior neck surgery reroutes lymphatic spread patterns.

Whole-organ sections at 3- to 5-mm intervals of 19 radical neck dissection specimens for 14 oral cavity, 3 oropharyngeal, and 2 laryngeal cancers were reported by Toker.[135] The submandibular area was skipped in three cases of anterior oral cancer, and, in three cases, the upper jugular chain was skipped. There were no metastases in intervening soft tissues between the primary tumor and lymph nodes.

Well-lateralized lesions spread to ipsilateral neck lymph nodes. Lesions on or near the midline and lateralized tongue and nasopharyngeal lesions may spread to both sides, but they tend to spread to the side occupied by the bulk of the lesion. Large nodal masses may produce obstruction of the lymphatic vessels, and tumor cells may be identified in afferent lymphatics.[36] Theoretically, large clinically positive lymph nodes in the neck could cause lymphatic blockade and detour tumor to the opposite neck even if the primary lesion is well-lateralized. Obstruction of the lymphatic pathways caused by surgery or radiation therapy may also shunt the lymphatic flow to the opposite side of the neck. This shunting occurs mainly through anastomotic channels in the submental area.[36]

When lateralized primary lesions metastasize contralaterally, the subdigastric node is the one most commonly involved. Occasionally, the subdigastric node may be bypassed, in which case the midjugular or low jugular chain is most often affected. When lymph node metastases appear in an unexpected distribution, a careful search must be made for a second primary tumor. The lymphatic collecting trunks empty into the venous system at the root of the neck, but, rarely, retrograde lymph node metastases into the ipsilateral axilla may be seen, usually in association with involvement of the lower neck nodes.

Extracapsular Spread

Snow and coworkers[124] reviewed 326 radical neck dissection specimens. Extracapsular spread was observed in 23% of nodes less than 1 cm in diameter, 53% of nodes 2 to 3 cm, and 74% of nodes larger than 3 cm.

Myers and Johnson[100] reviewed 177 radical neck dissections and reported extracapsular spread in 65% of lymph nodes less than 3 cm in diameter. Extracapsular spread was associated with about a 50% decrease in survival rates; survival was only slightly better with pathologically negative lymph nodes than with positive lymph nodes and no extracapsular spread.

The number of involved lymph nodes does not correlate with the risk of extracapsular spread.

Impact of Neck Stage on Local Control by Radiation Therapy

Four reports have noted an inverse relation between the extent of neck disease and local control for squamous cell carcinomas of the supraglottic larynx and oropharynx treated with radiation therapy.[54,136,139,140] However, Mendenhall and colleagues[85] reviewed 526 squamous cell

TABLE 6-3. Percentage of Clinically Detected Nodal Metastases on Admission, by T Stage (2044 Patients)

Primary Site	Stage	Nodal Metastases (%) N0	N1	N2–3
Oral tongue*	T1	86	10	4
	T2	70	19	11
	T3	52	16	31
	T4	24	10	66
Floor of the mouth*	T1	89	9	2
	T2	71	18	10
	T3	56	20	24
	T4	46	10	43
Retromolar trigone or anterior tonsillar pillar†	T1	88	2	9
	T2	62	18	20
	T3	46	21	33
	T4	32	18	50
Soft palate†	T1	92	0	8
	T2	64	12	24
	T3	35	26	39
	T4	33	11	56
Tonsillar fossa†	T1	30	41	30
	T2	32	14	54
	T3	30	18	52
	T4	10	13	76
Base of the tongue†	T1	30	15	55
	T2	29	14	56
	T3	26	23	52
	T4	16	8	76
Oropharyngeal walls†	T1	75	0	25
	T2	70	10	20
	T3	33	22	44
	T4	24	24	52
Supraglottic larynx‡	T1	61	10	29
	T2	58	16	26
	T3	36	25	40
	T4	41	18	41
Hypopharynx§	T1	37	21	42
	T2	30	20	49
	T3	21	26	54
	T4	26	15	58
Nasopharynx#	T1	8	11	82
	T2	16	12	72
	T3	12	9	80
	T4	17	6	78

* T stage defined by Lindberg.[67]
† T stage defined by Fletcher and coworkers.[40]
‡ T stage defined by Fletcher and coworkers.[41]
§ T stage defined by MacComb and coworkers.[71]
# T stage defined by Chen and Fletcher.[23]
Note: M. D. Anderson Hospital data; patients treated between 1948 and 1965.
(Lindberg R. Distribution of cervical lymph node metastases from squamous cell carcinoma of the upper respiratory and digestive tracts. Cancer 1972;29:1447)

carcinoma cases and could not confirm this finding. The local control rates for several head and neck sites are shown in Table 6-4. There was no evidence for a decrease in local control by radiation therapy with clinically positive as compared with clinically negative necks. Richard and coworkers[115] also could find no difference in local control related to N stage.

Prognosis Related to Distribution of Lymph Nodes in the Upper Neck Versus the Lower Neck

It is a commonly accepted observation that, stage for stage, clinically or pathologically positive lymph nodes in the lower neck represent a grave prognosis with few survivors.[51,60,66] However, the report by Berger and Fletcher[13] did not show an increased incidence of distant metastasis with involved lower neck nodes for squamous cell carcinoma of the nasopharynx, base of tongue, and tonsillar fossa. Ellis and colleagues[32] at the University of Florida reviewed 455 patients with squamous cell carcinoma who were treated with radiation therapy with or without neck dissection to determine the effect of clinically positive lymph nodes below the level of the thyroid notch. The incidence of distant metastasis was greater for metastatic adenopathy in the lower neck, and this was reflected in a lower 5-year cause-specific survival rate (Tables 6-5 through 6-8). The primary site and T stage had relatively little influence on the rate of distant metastasis. The risk of distant metastasis by therapeutic group is shown in Table 6-9.

GENERAL PRINCIPLES FOR MANAGEMENT OF THE NECK

The spread of tumor to the regional lymphatics follows a reasonably predictable pattern so that surgery, radiation therapy, or both combined can produce a high rate of neck control with acceptable morbidity. The role of chemotherapy in the management of the neck is considered experimental, and only the use of radiation therapy and surgery is discussed in this chapter.

Management of the Clinically Negative Neck

The published incidence of subclinical disease in the regional lymphatics when the neck is clinically negative is shown in Table 6-2. *Subclinical disease* refers to disease statistically known to be present but that cannot be seen or palpated in areas accessible to physical examination nor seen on highly efficient imaging studies. Table 6-10 shows the relative risk for subclinical disease related to T stage after elective modified neck dissection.[19]

A policy of wait and see may be adopted for N0 necks to avoid unnecessary treatment, and the neck may be successfully treated in about 60% if clinically positive nodes appear. However, even though the delayed neck treatment may be judged successful, these patients are at an increased risk to develop distant metastasis and have a poorer prognosis.[82,101] A positive lymph node that remains in the neck acts as a focus for dissemination to other lymph nodes and to distant sites. For patients presenting with a clinically negative neck, Jesse and coworkers[58] reported an 11% incidence of distant metastasis in patients whose neck became positive compared with 3% for those whose neck remained controlled (Table 6-11). Northrop and colleagues[101] reported that for patients

TABLE 6-4. The Impact of Neck Stage on Local Control Following Irradiation: Overall Local Control as a Function of N Stage (526 Patients)

T Stage	N Stage N0	N1	N2	N3	Total N+	N0 vs N+ (*P* value)
T1	43/48 (90%)	9/12 (75%)	6/7	7/8	22/27 (81%)	.258
T2	81/113 (72%)	27/39 (69%)	26/34 (76%)	14/24 (58%)	67/97 (69%)	.397
T3	23/48 (48%)	20/31 (65%)	23/38 (61%)	27/42 (64%)	70/111 (63%)	.054
T4	6/20 (30%)	8/15 (53%)	5/17 (29%)	9/30 (30%)	22/62 (35%)	.429

(Mendenhall WM, Parsons JT, Amdur RJ, Spangler AE, Williams TR, Cassisi NJ, Million RR. Squamous cell carcinoma of the head and neck treated with radiation therapy: the impact of neck stage on local control. Int J Radiat Oncol Biol Phys 1988;14:251)

TABLE 6-5. 5-Year Risk of Distant Metastasis as a Function of Neck Stage and Node Location (455 Patients)*

N Stage	Upper Neck Only (%)	Lower Neck ± Upper Neck (%)	*P* Value
N1	12	34	.129
N2A	19	55	.230
N2B	21	22	.127
N3A	45	71	.024
N3B	19	35	.022

* Calculated by the life-table method.
(Ellis ER, Mendenhall WM, Rao PV, Parsons JT, Spangler AE, Million RR. Does node location affect the incidence of distant metastases in head and neck squamous cell carcinoma? Int J Radiat Oncol Biol Phys 1989;17:295)

TABLE 6-6. Incidence of Distant Metastasis as a Function of Neck Stage and Node Location in 256 Patients Who Were Continuously Disease-Free Above the Clavicles*

N Stage	Upper Neck Only	Lower Neck ± Upper Neck	*P* Value
N1	6/79 (8%)	1/4 (25%)	.302
N2A	3/20 (15%)	1/3 (33%)	.453
N2B	5/31 (16%)	4/29 (14%)	≥.500
N3A	3/12 (25%)	3/6 (50%)	.294
N3B	3/34 (9%)	10/38 (26%)	.053

* Calculated by the direct method.
(Ellis ER, Mendenhall WM, Rao PV, Parsons JT, Spangler AE, Million RR. Does node location affect the incidence of distant metastases in head and neck squamous cell carcinoma? Int J Radiat Oncol Biol Phys 1989;17:295)

TABLE 6-7. Incidence of Distant Metastasis as a Function of T Stage and Node Location (455 Patients)*

T Stage	Upper Neck Only	Lower Neck ± Upper Neck	Total
T1	6/23 (26%)	5/13 (38%)	11/36 (31%)
T2	12/90 (13%)	15/52 (29%)	27/142 (19%)
T3	15/121 (12%)	14/53 (26%)	29/174 (17%)
T4	12/68 (18%)	8/35 (23%)	20/103 (19%)

* Calculated by the direct method.
(Ellis ER, Mendenhall WM, Rao PV, Parsons JT, Spangler AE, Million RR. Does node location affect the incidence of distant metastases in head and neck squamous cell carcinoma? Int J Radiat Oncol Biol Phys 1989;17:295)

TABLE 6-8. 5-Year Cause-Specific Survival as a Function of Neck Stage and Node Location (455 Patients)*

Neck Stage	Upper Neck Only (%)	Lower Neck ± Upper Neck (%)	*P* Value
N1	71	36	.076
N2A	48	45	.273
N2B	45	51	≥.500
N3A	54	13	.007
N3B	49	37	.027

* Calculated by the life-table method.
(Ellis ER, Mendenhall WM, Rao PV, Parsons JT, Spangler AE, Million RR. Dose node location affect the incidence of distant metastases in head and neck squamous cell carcinama? Int J Radiat Oncal Biol Phys 1989;17:296)

TABLE 6-9. Probability of Distant Metastasis in Different Prognostic Subgroups

Prognostic Group	Probability (%)
Neck stage N1 or N2B, treated with RT and neck dissection, with nodes located in the upper neck alone and no local–regional recurrence	4
Neck stage N1 or N2B, treated with RT and neck dissection, with nodes located in the lower neck and possibly the upper neck, with local–regional recurrence, or with both	10
Neck stage N2A or N3B, treated with RT with or without neck dissection, or neck stage N1 or N2B, treated with RT alone; with nodes located in the upper neck alone and no local–regional recurrence	11
Neck stage N2A or N3B, treated with RT with or without neck dissection, or neck stage N1 or N2B, treated with RT alone; with nodes located in lower neck and sometimes the upper neck, with local–regional recurrence, or with both	24
Neck stage N3A, treated with RT with or without neck dissection, with nodes located in the upper neck alone and no local–regional recurrence	32
Neck stage N3A, treated with RT with or without neck dissection, with nodes located in lower neck and possibly the upper neck, with local–regional recurrence, or with both	55

RT, radiation therapy.

(Ellis ER, Mendenhall WM, Rao PV, Parsons JT, Spangler AE, Million RR. Does node location affect the incidence of distant metastases in head and neck squamous cell carcinoma? Int J Radiat Oncol Biol Phys 1989;17:296)

with controlled N1 or N2 disease in the ipsilateral neck, the incidence of distant metastasis was 24% if the neck became positive, compared with 12% if the neck remained negative (Table 6-12). Votava and coworkers[138] reported similar results for N3 neck disease (Table 6-13).

Strong[131] reviewed patients with squamous cell carcinoma of the oral tongue managed by glossectomy and no elective neck treatment; 60% who developed neck disease died of cancer.

Harwood and coworkers[54] reported that elective irradiation of the N0 neck for supraglottic larynx carcinomas decreased the incidence of neck failure from 29% to 4% and decreased tumor deaths from 35% to 5%.

Elective neck treatment is indicated, therefore, when the associated morbidity is low. It has the added advantage of giving complete treatment initially and simplifying the follow-up neck examinations because of its high success rate.

It can be easily demonstrated that elective neck treatment markedly reduces the subsequent appearance of neck disease. The effect on the overall survival rate is small, however, because about 60% of those who subsequently develop neck node metastases are permanently salvaged. The survival advantage of elective neck treatment is offset by failures at the primary site, by second primaries of the head and neck, and by intercurrent disease. A randomized trial would require a large number of patients to detect a survival benefit.[80,92]

The estimated number of patients required for a randomized trial of elective lymph node irradiation or elective neck dissection to show a difference in deaths due to neck recurrence alone at the 0.05 significance level is shown in Table 6-14.[80] Patients were divided into three risk groups. The risk of occult disease in the clinically negative neck was estimated to be 15% for risk group I, about 25% for risk group II, and 35% or greater for risk group III. It was estimated that the incidence of neck failure with elective neck irradiation would be about 5% of the total population treated. With careful observation, about 60% of the patients who develop disease in the neck with the primary tumor controlled are salvaged. The number of evaluable patients would need to be increased by 50% to allow for about a 35% rate of uncontrolled primary lesions and 15% rate of death due to intercurrent disease. It can be seen from Table 6-14 that the probability of death from neck recurrence as the only cause of failure is small when the risk of occult disease is small. However, for certain primary sites (eg, base of tongue, hypopharynx), the risk of subclinical disease approaches 50% and is often a bilateral risk, so that a survival advantage could be shown with a large enough study.

TABLE 6-10. Elective Modified Neck Dissection: Incidence of Nodal Metastasis by T Classification and Site

	TX, T1, T2	T3–4	Total
Oral tongue	6/29 (20.7%)	6/19 (31.6%)	12/48 (25.0%)
Floor of mouth	8/43 (18.6%)	5/19 (26.3%)	13/62 (21.0%)
Lower gum	3/26 (11.5%)	2/15 (13.3%)	5/41 (12.2%)
Buccal mucosa	0/7 (0.0%)	0/3 (0.0%)	0/10 (0.0%)
Retromolar trigone	4/11 (36.4%)	4/12 (33.3%)	8/23 (34.8%)
Base of tongue	0/5 (0.0%)	5/10 (50.0%)	5/15 (33.3%)
Pharyngeal wall	1/5 (20.0%)	5/8 (62.5%)	6/13 (46.2%)
Glottic larynx	3/14 (21.4%)	8/57 (14.0%)	11/71 (15.5%)
Supraglottic larynx	4/13 (30.8%)	20/80 (25.0%)	24/93 (25.8%)
Pyriform sinus	2/3 (66.7%)	16/29 (55.2%)	18/32 (56.3%)

(Modified from Byers RM, Wolf PF, Ballantyne AJ. Rationale for elective modified neck dissection. Head Neck Surg 1988;10:165)

TABLE 6-11. Risk of Distant Metastasis Related to Initial Neck Control: Primary Sites in Oral Cavity; Clinically Negative Neck; No Elective Neck Treatment; Primary Lesion Controlled

Patients	Neck Control	With Distant Metastases (%)
387	Neck remained negative	3
94	Neck became positive	11

(Data fram Jesse RH, Berkley HT, Lindberg RD, Fletcher GH. Cancer of the oral cavity: is elective neck dissection beneficiol? Am J Surg 1970;120:505–508)

Although small randomized trials of elective neck treatment have been published,[35,137] none to date has come close to including the numbers of patients needed to confirm or deny the survival advantage. In such a trial, one is actually comparing the survival benefit in patients with neck metastases, so that, if 100 patients are randomized into each group and the risk for neck failure is 25 percent for each group, one is actually comparing the survival of the 25 patients in each group who have neck disease rather than the 100 patients in each group.[53]

The advantages of elective neck treatment lie not only in a small survival advantage but in the practical advantages of completing the therapy at the first instance. Observation requires close follow-up to detect neck failures, and salvage therapy is almost always more morbid than elective therapy even when successful. When the primary lesion is treated for cure by radiation therapy, the addition of elective neck irradiation is relatively free of side effects if properly planned to exclude as much normal tissue as possible. When the primary lesion is resected, the addition of a modified neck dissection incurs modest morbidity and is an acceptable alternative to the watch-and-hope plan.

Elective Neck Irradiation

A large volume of data supports the success of irradiation in eradicating subclinical disease in regional lymphatics.[8,14,38,68,82,88,91,95,101]

The results for elective neck irradiation when the primary lesion is controlled are shown in Tables 6-15 through 6-18.[8,14,82] The control of subclinical disease increases with increasing dose (Table 6-19).[39,80,86] The common causes of failure of elective neck irradiation are geographic miss, low dose, and failure to detect an involved lymph node that is 1.5 to 2 cm or larger. Geographic miss or failure to adequately encompass all the lymph nodes at risk is the most common cause of failure and, at the University of Florida, occurred most often in oral tongue and floor of the mouth lesions because of portals that were inadequate on the posterior border. Meoz and colleagues[89] reported similar results. Low dose most often occurs when a lymph node is near the edge or corner of the portal (ie, within 1 to 2 cm of the edge), and the dose may be 25% less than the dose in the central part of the treatment portal. Most so-called in-field failures result from the use of a portal that is slightly too small, which creates a situation in which a lymph node near the margin receives less than the specified dose. Subclinical disease in a lymph node could range from a barely detectable microscopic focus to a 2-cm node completely replaced by tumor but clinically undetectable. The dose required to eliminate subclinical disease may be different at the extremes of tumor size.

A dose analysis for control of palpable, 1- to 2-cm, clinically positive lymph nodes shows nearly 100% control with a dose of 6000 cGy given over 6 weeks. Some 1- to 2-cm involved masses are missed on palpation, and a radiation dose of 5000 cGy cures some masses of this size. However, if a lymph node region happens to receive 6000 cGy over 6 weeks, the chance of control is high even if a 2-cm involved node is missed on examination. Since the advent of CT examination of the neck, we have diagnosed obvious, 1- to 2-cm, CT-positive lymph nodes that could not be felt on reexamination. Fortunately, most of these positive lymph nodes occur in the first-echelon drainage area, which would receive 6000 cGy over 6 weeks as part of the treatment directed to the primary lesion. The first-echelon, high-risk lymph nodes lie in the middle of the primary portals for lesions of the nasopharynx, oropharynx, larynx, and hypopharynx and therefore receive more than an adequate dose. However, some of the first-echelon lymph nodes for oral cavity lesions lie near the posterior border of the primary portals, and the dose to the primary portals is often in the range of 4500 to 5000 cGy because part of the treatment is given by interstitial implant or intraoral cone. If the primary lesion recurs, there is a renewed chance for lymphatic spread, and the neck is at considerable risk even if elective neck irradiation has been given.

TABLE 6-12. Risk of Distant Metastasis Related to Initial Neck Control: Primary Sites in Oral Tongue, Floor of Mouth, and Faucial Arch; N1, N2A, N2B Neck Disease; Primary Lesion Controlled

Patients	Neck Control	With Distant Metastases (%)
134	Neck controlled by initial treatment	12
46	Neck not controlled by initial treatment	24

(Data from Northrop MF, Fletcher GH, Jesse RH, Lindberg RD. Evolution of neck disease in patients with primary squamous cell carcinoma of the oral tongue, floor of mouth, and palatine arch, and clinically positive neck nodes neither fixed nor bilateral. Cancer 1972;29:23–30)

TABLE 6-13. Risk of Distant Metastasis Related to Initial Neck Control: Primary Sites in Oral Cavity and Faucial Arch; N3A, N3B Neck Disease

Patients	Neck Control	With Distant Metastases (%)
20	Primary and neck controlled by initial treatment	5
45	Primary or neck not controlled by initial treatment	31

(Dato from Votava C Jr, Fletcher GH, Jesse RH Jr, Lindberg RD. Management of cervical nodes, either fixed or bilateral, from squomous cell carcinoma of the oral cavity and faucial arch. Radiology 1972;105:417–420)

TABLE 6-14. Estimated Risk of Isolated Neck Node Recurrence and Subsequent Death as a Function of Risk Group and Use of Elective Neck Irradiation (ENI)

Risk Group	ENI	Neck Failure Rate (%)	Dead of Neck Recurrence Alone* (%)	Evaluable Patients Required for a Randomized Trial†	Estimated Total Patients for Trial (+50%)
I	No	15	5	404	606
	Yes	5	2		
II	No	25	8	142	213
	Yes	5	2		
III	No	35	12	60	90
	Yes	5	2		

* Estimated salvage of two thirds.
† Number of evaluable patients required to show the difference in "dead of neck recurrence alone" at the .05 significance level. The total number of patients in the trial would need to be increased by about 15% for death due to intercurrent disease and at least 35% for uncontrolled primary lesions.
(Mendenhall WM, Million RR. Elective neck irradiation for squamous cell carcinoma of the head and neck: analysis of time-dose factors and causes of failure. Int J Radiat Oncol Biol Phys 1986;12:746)

TABLE 6-15. Efficacy of Elective Neck Irradiation (ENI) With Primary Tumor Controlled (125 Patients)

Primary Stage	Patients With Neck Controlled/ Patients With Primary Lesion Controlled		
	No ENI	Partial ENI	Whole ENI
T1	11/12	17/18	9/10
T2	6/8	17/17	22/22
T3	0/1	10/10	18/18
T4	1/1	5/5	3/3
TOTAL	18/22 (82%)*	49/50 (98%)*	52/53 (98%)*

* $P = .01$, using exact test procedures.[1]
Note: University of Florida data; patients treated October 1964 to June 1976; minimum 2-year follow-up.
(Mendenhall WM, Million RR, Cassisi NJ. Elective neck irradiation in squamous cell carcinoma of the head and neck. Head Neck Surg 1980;3:16)

TABLE 6-16. Comparison of Partial and Whole Neck Irradiation* in Squamous Cell Carcinomas of the Nasopharynx, Tonsillar Fossa, Base of Tongue, and Faucial Arch

	Patients	Stage N3 (%)	Neck Failures in Areas Initially Clinically Negative† (%)
Partial neck irradiation	185	6.5	12
Whole neck irradiation	284	35	2.5

* Radical neck dissection was added after radiation therapy in 24 patients with partial neck irradiation and in 58 patients with whole neck irradiation.
† Primary lesions and initial clinically positive neck disease were controlled.
(Data from Berger DS, Fletcher GH, Lindberg RD, Jesse RH Jr. Elective irradiation of the neck lymphatics for squamous cell carcinomas of the nasopharynx and oropharynx. Am J Roentgenol Radium Ther Nucl Med 1971;111:66–72)

TABLE 6-17. Failure of Initial Ipsilateral Neck Treatment in Patients With Carcinoma of the Tonsillar Fossa, Base of Tongue, Supraglottic Larynx, or Hypopharynx (596 Patients)

Treatment	Stage							
	N0			N1	N2A	N2B	N3A	N3B
	No Treatment	Partial	Complete					
Irradiation		15%	2%	15%	27%	27%	38%	34%
Surgery	55% (16/29)	35%	7%	11%	8%	23%	42%	41%
Combined		20%	0%	0%	0%	0%	23%	25%

Note: M. D. Anderson Hospital data; patients treated between 1948 and 1967.
(Adapted from Barkley HT Jr, Fletcher GH, Jesse RH, Lindberg RD. Management of cervical lymph node metastases in squamous cell carcinoma of the tonsillar fossa, base of tongue, supraglottic larynx, and hypopharynx. Am J Surg 1972;124:464)

TABLE 6-18. Cervical Metastasis Appearing in the Contralateral N0 Neck % in Patients With Carcinoma of the Tonsillar Fossa, Base of Tongue, Supraglottic Larynx, or Hypopharynx (596 Patients)

	Stage of Ipsilateral Neck				
Treatment	N0	N1	N2A	N2B	N3A
Radiation	4%	2%	9%	7%	0%
Surgery	25%	17%	23%	43%	33%
Combined	0%	0%	0%	11%	0%

Note: M. D. Anderson Hospital dota; patients treoted between 1948 and 1967.

(Adapted from Barkley HT Jr, Fletcher GH, Jesse RH, Lindberg RD. Management of cervical lymph node metastases in squamous cell carcinoma of the tonsillar fossa, base of tongue, supraglottic larynx, and hypopharynx. Am J Surg 1972;124:466)

Elective neck irradiation is not recommended for selected superficial oral cavity lesions in which the estimated risk of subclinical disease in the lymph nodes is small (less than 10%), because the external-beam portals required to irradiate the submandibular and subdigastric nodes must include a large amount of normal mucosa and most of both parotid glands.[88] However, if the medical condition of the patient would make future neck surgery dangerous, it is prudent to treat the neck electively.

For the patient with a lesion of the floor of the mouth or oral tongue who has no clinically evident neck disease, elective neck irradiation includes the lower neck even though the risk is small. The decision to treat only one or both sides of the neck is made individually for these patients.

Elective neck irradiation usually includes the entire neck on both sides for lesions of the nasopharynx, oropharynx, hypopharynx, and supraglottic larynx. Well-lateralized lesions of the tonsillar region and retromolar trigone require only ipsilateral neck treatment. Prior neck surgery, including biopsies, even if many years before cancer diagnosis, indicates treatment of the opposite neck. Large metastatic masses in the neck can theoretically cause lymphatic vessel obstruction with rerouting of flow to the opposite side of the neck; there are no data for the likelihood of this occurrence.

TABLE 6-19. Approximate Control Rate of Subclinical Squamous Cell Carcinoma in Neck Lymph Nodes by Dose

Dose	Approximate Efficiency (%)
3000 cGy/3 wk	70
4000 cGy/4 wk	80–90
4500–5000 cGy/5 wk	95
4050 cGy/3 wk	95
3000 cGy/2 wk	95
6000 cGy/6 wk	99

(Data from Fletcher GH. Irradiation of subclinical disease in the draining lymphatics. Int J Radiat Oncol Biol Phys 1984;10:939–942; Mendenhall WM, Million RR. Elective neck irradiation for squamous cell carcinoma of the head and neck: analysis of time-dose factors and causes of failure. Int J Radiol Oncol Biol Phys 1986;12:741–746; and Mendenhall WM, Parsons JT, Million RR. Elective lower neck irradiation: 5000 cGy/25 fractions versus 4050 cGy/15 fractions. Int J Radiat Oncol Biol Phys 1988;15:439–440)

The results of partial neck irradiation as compared with whole neck irradiation for lesions originating in the nasopharynx, tonsillar fossa, base of the tongue, and faucial arch were shown in Table 6-16.[14] Partial neck irradiation was usually prescribed for patients with earlier stages of neck disease, in which case the neck was not completely irradiated. Twelve percent (22 patients) developed new lymph node disease in areas initially negative when both the primary lesion and the clinically positive nodes (if present) were controlled. Three patients had recurrences in electively irradiated areas, and the other 19 developed recurrences either at the edge of the treatment portal or well outside the irradiated field. In the group of 284 patients with whole-neck irradiation, of whom 35% had N3 neck disease, only 7 patients had recurrences in areas initially clinically negative; 5 recurrences were within electively irradiated areas, and 2 were outside irradiation portals in the submental area.

The justification for elective irradiation of the lower jugular and supraclavicular nodes is emphasized by Sagerman and coworkers,[121] who reviewed 72 patients given preoperative irradiation, 5000 cGy over 5 weeks, for stage III and IV glottic, supraglottic, and pyriform sinus cancers. Thirty-one patients were treated with only lateral opposing portals that did not include the low neck, and 41 had similar portals but also an added 5000 cGy through a separate low neck portal. Ten (32%) of the 31 patients treated with the two-field technique died with a recurrence, whereas only 4 (10%) of the 41 patients who had the added low neck treatment developed a recurrence. The complication rate was no different in the two groups.

Elective Neck Dissection

Surgeons have argued for many years over the relative benefit of elective neck dissection as compared with observation.[58] It is a difficult decision to recommend an elective radical neck dissection, with the resulting cosmetic and functional losses, unless the potential benefit is considerable. However, modified operations have reduced this morbidity and work as well as radical neck dissection for subclinical (N0) disease or for clinically positive mobile lymph nodes without extranodal extension.*[16] Modified neck dissections are 90% to 95% efficient for the clinically negative neck and produce relatively few side effects; postoperative irradiation may be added for evidence of extracapsular spread or the finding of more than two positive nodes in the specimen. Recur-

* Dr. George Crile described a functional neck dissection in 1906. He indicated that only the regional lymphatics were removed if there were "no palpable glands," and, in the discussion following his presentation to the American Medical Association, he stated that the sternomastoid muscle and internal jugular vein were removed only when neck metastases had already occurred.[26] Bocca credits O. Suarez of Argentina (1963) for describing the technique of conservative neck dissection.[132]

rence in the dissected neck after elective neck dissection is simply a failure to remove all the nodes at risk or unrecognized extranodal spread.[18] Disadvantages to elective neck dissection are the extra cost, the extra operating time, and the performance of a procedure that helps in only a small percentage of cases.

One disadvantage of elective neck dissection occurs when a recurrence takes place at the primary site. The usual lymphatic routes of spread have been interrupted so that the spread is either to bizarre ipsilateral sites (eg, occipital, parotid area, facial lymph nodes) or to contralateral areas or both.

For early lesions of the oral cavity, an elective supraomohyoid or suprahyoid neck dissection on one or both sides has been popular in past years because the risk of disease in the undissected portion of the neck is low. A complete functional neck dissection has replaced the supraomohyoid neck dissection in recent years because the operative time and morbidity are essentially the same. Partial neck dissection is definitely not regarded as sufficient treatment for lesions of the oropharynx, larynx, or hypopharynx (see Table 6-17).

Management of the Clinically Positive Neck

The rate of neck failure by N stage and therapeutic category reported from M. D. Anderson Hospital is shown in Table 6-17.[8] For the combined treatment group, the irradiation preceded the neck operation if the primary site was to be treated by radiation therapy or if a node was fixed or borderline resectable; the operation preceded the irradiation if the primary site was to be treated surgically.

Primary Tumor Managed by Operation

Neck dissection is sufficient treatment to the ipsilateral neck for pathologic stage N1 or N2A (1 to 6 cm), single, mobile metastatic lymph nodes if there is no extracapsular extension. Postoperative radiation therapy is considered for invasion through the capsule, multiple (more than two) positive lymph nodes (especially when found at multiple levels), and masses 6 cm or greater. The contralateral neck is frequently at risk when the ipsilateral neck is positive, and either elective neck dissection or radiation therapy should be considered for subclinical disease (see Table 6-18).

Patients with borderline resectable or unresectable neck disease secondary to extension through the capsule and fixation to the neurovascular bundle are treated first with irradiation. The dose administered to the primary lesion is usually limited to 4000 to 5000 cGy. This is followed by a boost through a reduced field to the neck node mass, attempting to use radiation portals that avoid further irradiation of the primary site. The dose to a fixed node is boosted to 6000 to 8000 cGy. Lower doses do not effect sufficient tumor kill and regression to allow the development of adequate surgical margins. It is necessary to use techniques that spare the skin and subcutaneous tissues.[93] Resection of the primary lesion and appropriate neck dissection follow in 4 to 8 weeks. The large neck mass develops a thick capsule, which aids dissection from the neurovascular bundle. Masses that abut or partially encircle the neurovascular bundle usually regress sufficiently for a plane of dissection. In a high proportion of cases, the lymph node becomes resectable, and, in close to one half of the cases, the pathologic specimen is negative for tumor.

Primary Tumor Managed by Radiation Therapy

When the primary lesion is to be treated by radiation therapy only, irradiation alone is sufficient for patients with small N1 (1 to 2 cm) disease, but irradiation should sometimes be combined with a neck dissection for large N1 (3 cm) disease; neck dissection is almost always considered for N2A or N3A disease. For primary tumors of the nasopharynx, the neck nodes are more curable. The decision to add neck dissection for multiple ipsilateral nodes is individualized, based on the diameter of the largest node, the multiplicity of palpable nodes, and their distribution within the neck. For example, the neck may be staged N2B on the basis of a 2-cm subdigastric node and two 1-cm nodes in the upper neck; this neck might be treated with radiation therapy alone. Another patient with stage N2B might have small nodes located in the upper, mid, and lower neck and be better managed by adding neck dissection rather than administering a high dose to the entire neck. Yet another patient with N2B disease might have a 3- to 4-cm neck node and several other small nodes, and neck dissection should be considered. Each side of the neck is considered separately when disease is bilateral; if possible, one side of the neck should be treated by irradiation alone. Bilateral neck dissections after radiation therapy may be staged or simultaneous. Most reports show a higher complication rate with simultaneous neck dissections, and the patient may require an elective tracheostomy, especially if the larynx has been irradiated. If enlarged nodes disappear completely and early during a course of radiation therapy, the likelihood of control by irradiation alone is improved and neck dissection may be withheld. However, if there is any question about complete regression, it is safer to add the neck dissection 4 to 8 weeks after radiation therapy, because the detection of neck node recurrence after high-dose radiation therapy is difficult and salvage attempts are generally morbid and unsuccessful. Mendenhall and coworkers[83] reported only a 5% rate of successful salvage, and Bernier and Bataini[15] reported a 1% success rate for the management of neck recurrence after irradiation alone for clinically positive neck nodes. Large, fixed nodes (greater than 5 to 6 cm) may receive 6000 to 8000 cGy before neck dissection; half of the specimens show no viable tumor, and quite a few patients have the disease controlled in the neck (Fig. 6-36). Planned neck dissection 4 to 8 weeks after twice-daily radiotherapy (7400 to 8160 cGy) has been accomplished with acceptable morbidity and no operative mortality.

Radiotherapy alone for large-volume N2-N3 neck disease has several disadvantages: (1) The rate of disease control in the neck is poorer. (2) Detection of recurrence is more difficult because of the fibrosis produced by both the high dose of radiotherapy and the fibrous reaction in and about the neck node. (3) Salvage surgery is infrequently successful after a failure of radiotherapy alone and is attended by a relatively high incidence of wound complications.[81] (4) Paradoxically, the fibrosis produced in the soft tissues of the neck is actually greater in patients with large nodal masses who are cured by high-dose radiotherapy than in patients who receive similar

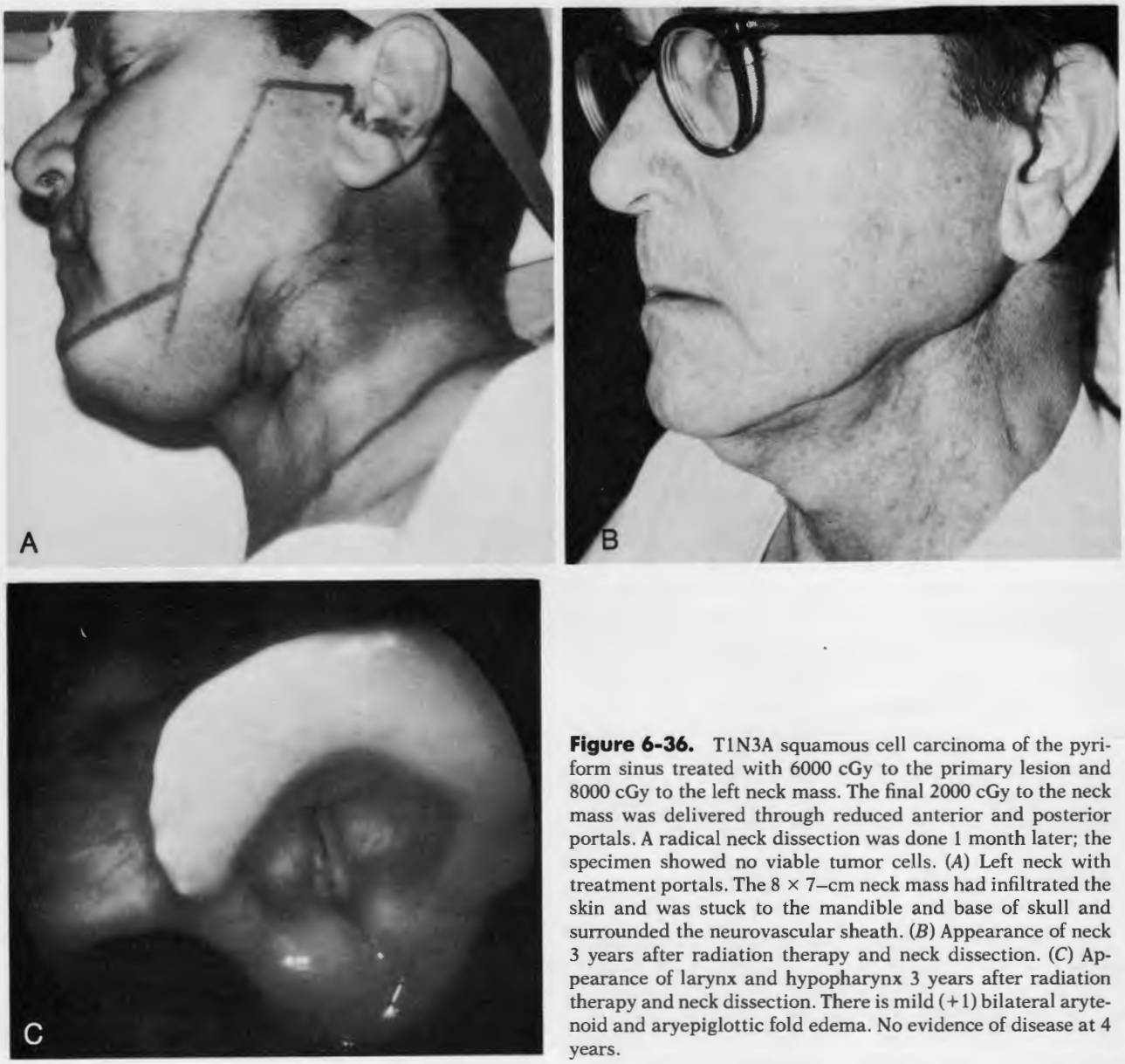

Figure 6-36. T1N3A squamous cell carcinoma of the pyriform sinus treated with 6000 cGy to the primary lesion and 8000 cGy to the left neck mass. The final 2000 cGy to the neck mass was delivered through reduced anterior and posterior portals. A radical neck dissection was done 1 month later; the specimen showed no viable tumor cells. (*A*) Left neck with treatment portals. The 8 × 7–cm neck mass had infiltrated the skin and was stuck to the mandible and base of skull and surrounded the neurovascular sheath. (*B*) Appearance of neck 3 years after radiation therapy and neck dissection. (*C*) Appearance of larynx and hypopharynx 3 years after radiation therapy and neck dissection. There is mild (+1) bilateral arytenoid and aryepiglottic fold edema. No evidence of disease at 4 years.

doses of radiotherapy followed by radical neck dissection. In the former group, entrapment and paralysis of cranial nerve XII by dense fibrosis in the upper neck may occur, whereas it is rarely seen when a neck dissection is added. The explanation appears to be that the fibrous stroma of the lymph node contributes to overall fibrosis in the neck when it is not surgically removed.

When the primary lesion is to be treated by radiotherapy, our preference is that the neck dissection follow radiotherapy. The advantages of this approach are several: (1) We have not considered it a good idea to perform neck dissection in the presence of an uncontrolled primary lesion because surgical interruption of the lymphatics may lead to contralateral or bizarre patterns of lymph node metastasis as a result of collateral or aberrant flow.[36] (2) For large lymph nodes, extranodal spread and fixation to the carotid sheath are rather common. After high-dose radiotherapy, the neck disease frequently becomes operable without carotid sacrifice. (3) If the neck dissection is performed before the radiotherapy, the radiotherapist is faced with the situation that he or she must chase surgical scars into areas that otherwise might not require treatment (eg, into the submandibular region). (4) Performance of the neck dissection first leads to a delay in treating the primary site. (5) There is little published information to show the results of neck dissection when performed before radiation therapy of the primary site (see Chap. 15). (6) A scenario that sometimes occurs is that a patient with an unknown primary carcinoma is treated with a neck dissection before referral for irradiation. In this circumstance, there is often postoperative edema of the ipsilateral hemilarynx, making difficult the determination of the primary site (eg, pyriform sinus or supraglottic larynx).

Performance of radiotherapy first does have the disadvantage of potentially increasing the risk of severe surgi-

TABLE 6-20. Comparison of Ultimate Local Control for Radiation Therapy (RT) Alone and RT Plus Planned Neck Dissection (ND) in Patients With Clinically Positive Neck Nodes (Controlled/Treated, 227 Patients)

	Local Control After RT*		Salvaged/ Attempted		Ultimate Local Control	
T stage	RT	RT + ND	RT	RT + ND	RT	RT + ND
T1	12/14 (86%)	7/8	0/1	0/1	12/14 (86%)	7/8
T2	29/40 (73%)	25/34 (74%)	1/8	3/5	30/40 (75%)	28/34 (82%)
T3	32/51 (63%)	23/33 (70%)	2/7	0/2	34/51 (67%)	23/33 (70%)
T4	10/39 (25%)	3/8	1/4	1/2	11/39 (28%)	4/8

* Continuous-course RT, once-o-doy or twice-o-day fractionation.
(Mendenhall WM, Parsons JT, Amdur RJ, Cassisi NJ, Million RR. Squamous cell carcinomo of the head and neck treated with radiotherapy: does planned neck dissection reduce the chance for successful surgical management of subsequent local recurrence? Head Neck Surg 1988; 10:304)

cal morbidity. A number of technical modifications, both radiotherapeutic and surgical, have been made through the years to minimize this problem as much as possible. In our own series of patients, we believe that the risks of this treatment sequence are outweighed by the benefits.

A question arises as to whether a planned neck dissection interferes with the surgical management of a subsequent local recurrence. Mendenhall and associates[84] studied this problem in a review of 227 patients with squamous cell carcinoma of the oropharynx, supraglottic larynx, and hypopharynx. Comparing those treated with radiation alone versus radiation therapy plus planned neck dissection, there was no difference in either the initial control of the primary site or the success rate of surgical salvage of a local recurrence (Table 6-20).

Management of the Neck After Excisional or Incisional Biopsy

Hayes Martin[77] and many who followed him taught that the injudicious biopsy of a cervical lymph node containing metastatic carcinoma for diagnosis before definitive therapy invariably lessened the chance for cure. In 1978, McGuirt and McCabe[78] reviewed the University of Iowa experience for 64 patients who had a cervical node excised or incised before definitive treatment. Rates of neck recurrence, distant metastasis, and wound necrosis were significantly higher in biopsied necks compared with those that had no biopsy (605 patients) or had biopsy at the time of definitive therapy (46 patients). There were no data regarding the use of irradiation in their analysis.

Parsons and colleagues[110] reviewed the University of Florida experience for 80 patients who had an open biopsy of a cervical lymph node before definitive therapy and who were treated with radiation therapy as the initial treatment followed in selected cases by neck dissection and in some cases by resection of the primary lesion. Regional control rates according to N stage are shown in Table 6-21. The 5-year cause-specific survival for 17 evaluable patients with a single node excised and who were treated by radiation therapy was 88%. The 5-year cause-specific survival for those with gross residual neck disease was 32% for those treated by only radiation therapy and 50% for those with a neck dissection added. These results were thought to be similar to those for stage III and IV patients without open biopsy, and it was concluded that radiation therapy should probably be the initial treatment after open neck node biopsy; neck dissection or resection of the primary tumor, or both, should follow, depending on the clinical situation.

Ellis and associates[31] updated the University of Florida experience in 1989 for incisional or excisional biopsy before definitive therapy. Sixty-six patients who had undergone an open neck biopsy before radiation therapy were compared with a control group of 442 patients with a clinically positive neck and no neck biopsy. The biopsy had no detrimental effect when radiation therapy was the initial treatment (Tables 6-22 through 6-25). In fact, there was a trend to improved neck control and survival rates and a lower probability of distant metastasis in some groups in spite of the fact that the biopsy group was pathologically staged and the no-biopsy group was clinically staged. The treatment results for 41 patients presenting after excisional biopsy of a single positive neck node (NX) were updated in 1990 (Mack Y, unpublished data, April 1990). These patients had no palpable disease remaining in the neck, and there was no residual tumor in the neck according to the surgeon and pathologist. The primary site was not found in 22 patients. The lymph node size based on description by the referring

TABLE 6-21. Neck Control in Heminecks After Biopsy According to Treatment Technique (Controlled/Treated)*

N Stage	RT Alone	RT + Radical Neck Dissection
NX	23/24 (96%)	0/0
N1–2	13/20† (65%)	6/7‡ (86%)
N3A	2/7 (29%)	5/8 (63%)

RT, radiation therapy.
* Minimum 2-year follow-up.
† Includes 3 N1, 2 N2A, 15 N2B patients.
‡ Includes 3 N2A, 4 N2B patients.
(Parsons JT, Million RR, Cassisi NJ. The influence of excisional or incisional biopsy of metastatic neck nodes on the management of head and neck cancer. Int J Radiat Oncol Biol Phys 1985;11:1450)

TABLE 6-22. Comparison of Neck Control at 5 Years With or Without Neck Biopsy Before Irradiation With or Without Neck Dissection (660 Heminecks)

	No Neck Biopsy		Neck Biopsy		
Hemineck Stage	Heminecks	Probability of Hemineck Control* (%)	Heminecks	Probability of Hemineck Control* (%)	Significance of Difference Between Curves
N1	253	87 ± 3	12	100†	$P = .22$
N2A	53	73 ± 8	15	93 ± 6	$P = .18$
N2B	218	78 ± 3	23	72 ± 11	$P = .86$
N3A	69	54 ± 7	17	81 ± 10	$P = .30$

* Results are given as of 5 years.
† No neck recurrences; all 12 heminecks censored at 1 month to 15 years 8 months.
(Ellis ER, Mendenhall WM, Rao PV, et al. Incisional or excisional neck-node biopsy before definitive radiotherapy, alone or followed by neck dissection. Head Neck 1991;13:179)

TABLE 6-23. Comparison of the Overall Risk of Distant Metastasis at 5 Years With and Without Neck Biopsy Before Irradiation With or Without Neck Dissection (508 Patients)*

	No Neck Biopsy		Neck Biopsy		
Neck Stage	Patients	Probability of Distant Metastasis† (%)	Patients	Probability of Distant Metastasis† (%)	Significance of Difference Between Curves
N1	130	14 ± 4	12	0‡	$P = .18$
N2A	34	25 ± 8	15	17 ± 11	$P = .42$
N2B	106	22 ± 5	9	11 ± 10	$P = .47$
N3A	38	47 ± 9	12	53 ± 19	$P = .60$
N3B	134	26 ± 5	18	31 ± 11	$P = .81$

* Patients were censored at death or latest follow-up only if they never manifested any evidence of distant metastasis.
† Results are given as of 5 years.
‡ All patients were censored, at 1 month to 15 years 8 months.
(Ellis ER, Mendenhall WM, Rao PV, et ol. Incisional or excisional neck-node biopsy before definitive radiotherapy, alone or followed by neck dissection. Head Neck 1991;13:179)

TABLE 6-24. Comparison of 5-Year Cause-Specific Survival by N Stage With and Without Neck Biopsy Before Irradiation (508 Patients)

	No Neck Biopsy		Neck Biopsy		
Neck Stage	Patients	Probability of Survival* (%)	Patients	Probability of Survival* (%)	Significance of Difference Between Curves
N1	130	67 ± 4	12	100†	$P = .08$
N2A	34	47 ± 9	15	75 ± 13	$P = .05$
N2B	106	45 ± 6	9	75 ± 15	$P = .09$
N3A	38	31 ± 8	12	35 ± 16	$P = .50$
N3B	134	40 ± 5	18	45 ± 14	$P = .21$

* Results are given as of 5 years.
† One death with disease present, at 7 years 2 months; 11 patients censored at 1 month to 15 years 8 months.
(Ellis ER, Mendenhall WM, Rao PV, et al. Incisional ar excisional neck-node biopsy before definitive radiotherapy, alone or followed by neck dissection. Head Neck 1991;13:180)

TABLE 6-25. Comparison of 5-Year Cause-Specific Survival by AJCC Stage With and Without Neck Biopsy Before Irradiation (508 Patients)

	No Neck Biopsy		Neck Biopsy		
Modified AJCC Stage	Patients	Probability of Survival* (%)	Patients	Probability of Survival* (%)	Significance of Difference Between Curves
III	110	68 ± 5	11	100†	$P = .05$
IVA	143	48 ± 5	35	66 ± 9	$P = .13$
IVB	189	38 ± 4	20	46 ± 13	$P = .20$

* Results are given as of 5 years.

† All patients censored, at 1 month to 15 years, 8 months.

(Ellis ER, Mendenhall WM, Rao PV, McCarty PJ, Parsons JT, Stringer SP, Cassisi NJ, Million RR. Incisional or excisional neck-node biopsy before definitive radiotherapy, alone or followed by neck dissection. Head Neck 1991;13:180)

physician or pathologist is shown in Table 6-26. Treatment was radiation therapy alone in 39 patients and radiation therapy plus neck dissection in 2 patients. A wide range of doses was delivered to the surgical bed because the dose was most often determined by the dose specified to the primary lesion rather than the neck. There were two neck failures. There were no failures in patients who had nodes excised from the jugular chain; the two failures were in patients who had nodes excised from the submental and submandibular area. Control rates for neck disease according to the original node diameter are shown in Table 6-26. The 5- and 10-year results are given in Table 6-27. The results are surprisingly good considering that 22 patients were stage III and 19 were stage IVA.

The M. D. Anderson Hospital experience with open cervical lymph node biopsy in 192 patients showed results similar to the University of Florida series.[116] Cause-specific survival curves are shown in Figure 6-37 for patients who had a neck biopsy with a known primary site (139 patients) or an unknown primary site (53 patients), and for 102 selected patients with neck biopsy and 204 matched controls without biopsy. Eighty-four percent of the patients with no residual neck disease (NX) and 92% of those with residual neck disease received radiation therapy as all or part of the treatment.

TABLE 6-26. Excisional Biopsy of a Single Neck Lymph Node (NX): Neck Control by Radiation Therapy (41 Patients)*

Node Size	Control of Disease in Neck†
≤2 cm	5/5
2.1–4 cm	19/20
4.1–6 cm	5/6
>6 cm	1/1
Unknown	6/6

* Two patients also had a neck dissection.

† Minimum 2-year to unlimited follow-up. Excludes 3 patients who died within 2 yeors without neck recurrence.

Note: University of Florida data; patients treated October 1964 to September 1987; analysis April 1990 by Yvonne Mack, MD.

Irradiation is recommended for the initial therapy after excisional or incisional biopsy. If the primary tumor is to be managed by radiation therapy and a single lymph node has been excised, radiation therapy alone is sufficient; 6000 cGy to the biopsy site is probably sufficient. If the mass has been incisionally biopsied, or if there is residual disease in the neck after excision of one of several nodes, neck dissection should be strongly considered after irradiation. If the primary site is to be managed by an operation, preoperative irradiation is recommended and the doses are individualized.

Although no adverse effect of an open neck-node biopsy was demonstrated by our analysis, we do not generally recommend an open neck-node biopsy before definitive therapy because it may complicate subsequent management and is often unnecessary. When a careful search for a mucosal head and neck primary lesion is unsuccessful, a needle biopsy of the suspicious neck node remains the initial procedure.

Recurrence in the Neck

Obvious recurrence of squamous cell carcinoma in the neck requires a repeat work-up to rule out local recurrence, a new head and neck primary, and distant metastases. CT or MRI should be included to assist with the

TABLE 6-27. Excisional Biopsy, Single Neck Lymph Node (NX) Followed by Radiation Therapy (41 Patients)*

	5 Years (%)	10 Years (%)
Actuarial absolute survival	77	60
Actuarial cause-specific survival	93	88
Local control	96	94
Neck control	95	95
Relapse-free survival	96	95

* Two patients also had neck dissections.

Note: University of Florida data; patients treated October 1964 to September 1987; analysis April 1990 by Yvonne Mack, MD.

diagnosis, to look for other involved nodes, to examine the anatomic extent of the nodal disease, and to help exclude another primary tumor. The various manifestations of posttreatment changes in the head and neck region are discussed in detail in Chapter 4. CT and MRI can sometimes detect lymphadenopathy that cannot be felt on physical examination after radiotherapy (see Fig. 6-32). Drainage patterns may be so altered that deeper lymph-node groups such as the retropharyngeal nodes, junctional nodes, and those in the tracheoesophageal groove are more likely to be involved with tumor and difficult to detect clinically.

It is frequently impossible to determine whether a mass in the submandibular space is related to radiation sialadenitis, obstructive sialadenitis, or an enlarged metastatic lymph node. CT can make this differentiation in some cases and help avoid delay in effective management. The morphology of the enlarged enhancing submandibular salivary gland differs greatly from that of an enlarged node containing a metastatic deposit (see Fig. 6-29).

The image of the neck varies tremendously based on the type of neck dissection done. It is relatively easy to evaluate the neck after radical neck dissection or if a myocutaneous flap has been used to close the wound. After functional neck dissection, the fatty envelope between the sternocleidomastoid and paraspinous muscles is no longer present, and the two muscle groups come to appose one another with the carotid and jugular vein in between (Fig. 6-38). This makes it difficult to detect subtle adenopathy deep to the sternocleidomastoid muscle with CT. MRI is useful in this setting because an enlarged node contrasts well with the muscle groups on T2-weighted or fat-suppressed images. When surgery and radiotherapy are combined in the neck, the effects are cumulative, and fairly extensive scar bands are visible. On a single study, it may be difficult to tell the difference between extensive scarring and recurrent tumor (see Chap. 4). MRI is probably more effective than CT for distinguishing recurrent tumor from scar. Imaging-directed biopsy can be used in questionable cases. An imaging-directed biopsy can be particularly helpful in reaching nodes that are inaccessible for histologic confirmation by other means. The treatment plan is individualized depending on prior surgery and radiation therapy. If there has been no prior neck treatment, the approach is similar to that used for the patient presenting initially with involved lymph nodes. If the patient has had only radiation therapy, neck dissection is considered; postoperative radiation therapy with electrons may be considered for small areas at high risk for recurrence. Unresectable recurrences in the surgically dissected neck are treated with radiation therapy with localized boosts with external beam or implant. Hyperthermia has been used in combination with radiation therapy for this situation with some good responses reported.

Single localized recurrences in the neck after neck dissection and full-dose irradiation may rarely be treated successfully by excision or implant.

Results of Treatment for Neck Recurrence

When neck nodes develop in a neck initially thought to be clinically negative, the salvage rate is about 60% if the primary tumor remains controlled. The salvage rate for recurrence in the dissected neck is low regardless of the therapy. The salvage rate for recurrence in the neck after only irradiation for clinically positive necks is 1% to 5%, and the morbidity of the salvage neck surgery is usually considerable.[15,83]

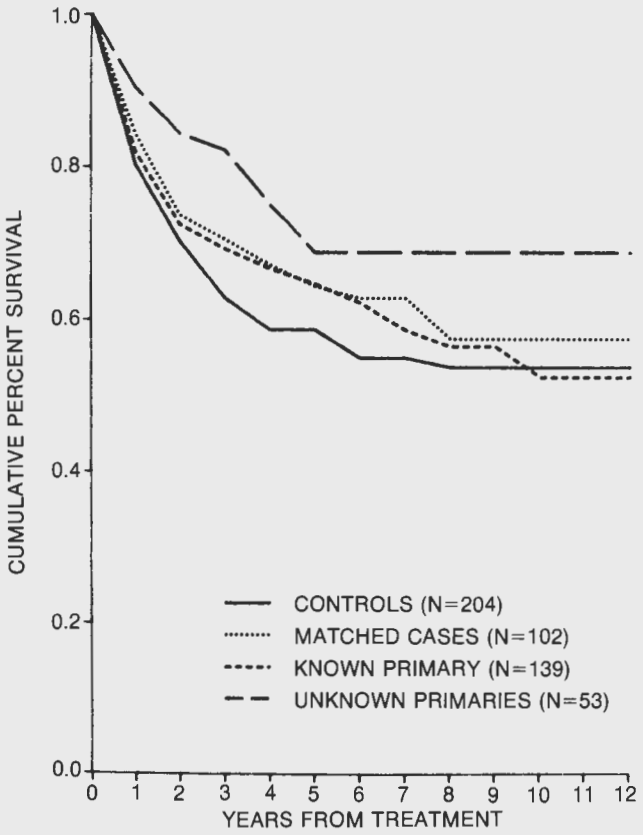

Figure 6-37. Cause-specific survival (product-limit method[61]) for 192 patients treated at M. D. Anderson Hospital with cervical node biopsy (139 with a known primary site and 53 with unknown primary site). In this series, 102 patients with a known primary site were matched with 204 control cases without neck node biopsy. (Robbins KT, Cole R, Marvel J, Fields R, Wolf P, Goepfert H. The violated neck: cervical node biopsy prior to definitive treatment. Otolaryngol Head Neck Surg 1986;94:606)

SURGICAL MANAGEMENT OF THE NECK

The concept of en bloc removal of regional lymph nodes has undergone multiple modifications and improvements in the nearly 90 years since first described by Crile in 1906.[49]

Regional Anatomy Pertinent to Neck Dissection

Arterial Supply to the Skin of the Neck and Its Influence on Neck Dissection Incisions

The incision that is selected for neck dissection is based, first of all, on whether the primary site is to be resected, because the exposure of the primary lesion governs the choice of incision. Many incisions are available to the surgeon, and each has advantages and disadvan-

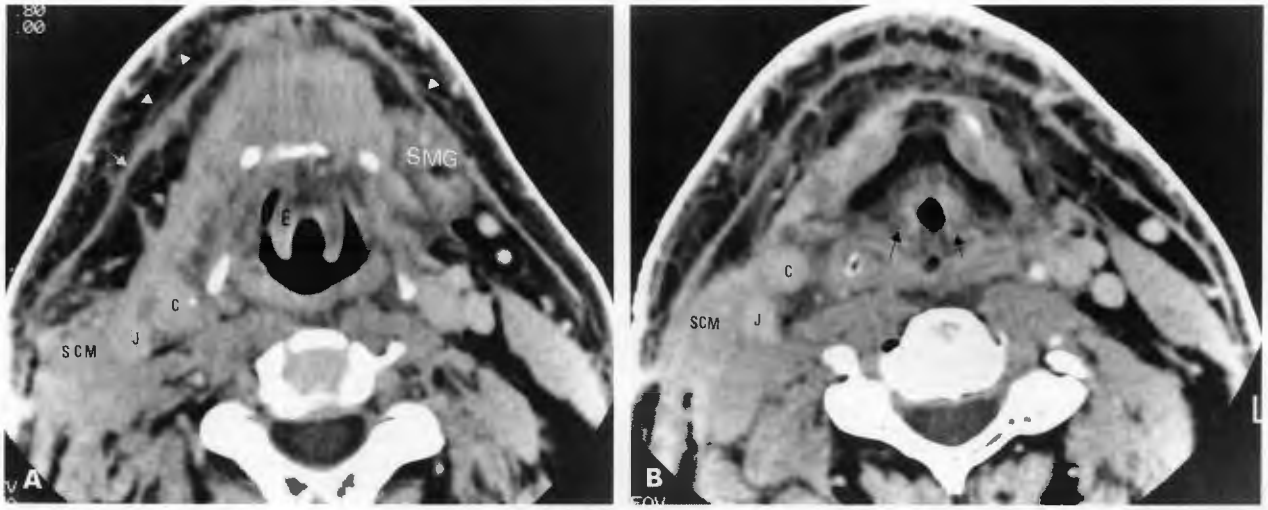

Figure 6-38. Typical changes in the neck after functional neck dissection and radiotherapy to doses over 7000 cGy. (*A*) The linear densities within subcutaneous and deeper fat (*arrowheads*) are manifestations of lymphedema or perilymphatic fibrosis. The platysma (*arrow*) is thickened. The submandibular gland on the right has been removed (SMG, contralateral remaining gland). The free margin of the epiglottis (E) is markedly thickened. The fatty envelope around the carotid artery (C) and jugular vein (J) is no longer visible (compared with the left side). The sternocleidomastoid muscle (SCM) remains. (*B*) The carotid and jugular are more easily seen between the sternocleidomastoid muscle and muscles of the floor of the neck. Thickening of the endolaryngeal soft tissues, especially the ayrepiglottic folds (*arrows*), is also a common finding after high-dose radiotherapy.

tages. Knowledge of the vascular supply to the cervical skin is an important factor in selecting the incision most likely to heal without necrosis, especially when prior radiation therapy has been administered. A simplified schematic of the arterial supply to the skin of the neck is provided in Figure 6-39, *center*.[45] The arterial supply tends to run in a superior–inferior direction. The facial, occipital, and transverse cervical arteries may occasionally require ligation during the operation. Numerous arterial loops are shown to be present on cadaver injection studies. The venous drainage proceeds from superior to inferior and is interrupted by any horizontal incision.[34]

The popular Hayes Martin incision (see Fig. 6-39, *upper left*) affords excellent anatomic exposure, but it places the trifurcate junction over the carotid and risks exposure and rupture of that vessel.[76] The MacFee incision (see Fig. 6-39, *upper right*) avoids a trifurcate junction, but it may not provide adequate exposure for a surgeon who is not experienced with the technique.[72] The cosmetic result is excellent. A neck incision commonly used by Cassisi and similar to that proposed by Ogura, Freund, Schobinger, Conley, and others (see Fig. 6-39, *lower left*) provides good exposure, minimal interruption of the blood supply, and satisfactory cosmetic result.[6,46,102] There is a small risk of wound dehiscence at the bifurcation, especially after radiation therapy. The vertical limb is placed far posterior so that there is virtually no need to dissect and elevate the posterior flap. The posterior flap is supplied with blood by the descending branch of the occipital artery from above and by the ascending branch of the transverse artery from below. In the event that radiation therapy has been used before surgery, this posterior flap receives little or no irradiation. Therefore, one has an essentially normal segment of skin to suture to the front flaps, and the trifurcation is posterior to the common carotid. The horizontal limb of the incision allows satisfactory exposure of the submaxillary and submental area. The vertical limb tends to drift anteriorly as it heals; as a result, its final position is somewhat farther forward than might be imagined, based on its initial position (Fig. 6-40). This modification in the neck incision is one of the changes that has enabled neck dissection to be performed without catastrophic complications after the delivery of high doses of radiation therapy (6000 to 8000 cGy) to large, fixed neck nodes.

The single-limb incision (Fig. 6-41) is the most commonly used incision for neck dissection at our institution. It avoids a trifurcate junction, which is especially useful in previously irradiated patients. Exposure of the submental region or the opposite neck is achieved by continuing the incision well across the midline and up the opposite sternocleidomastoid muscle if necessary. This incision is the most useful for access for second primary tumors or opposite neck recurrences, with the exception of those cases requiring a lip-splitting approach.

If the patient is to receive postoperative radiation therapy, the radiation oncologist must decide whether to cover the entire area of the surgical dissection. It is customary to include the entire surgical field, but incisions that extend far beyond the conventional radiation field require an increased volume of irradiation and minor changes in treatment planning. Although this can be done, especially when electron-beam therapy is available, it unnecessarily complicates the radiation therapy and should be avoided when possible.

Normal Venous Drainage of the Head and Neck

The intracranial and extracranial arrangement of the veins of the head and neck area is shown in Figure 6-42.[34]

Except for a few small veins around the larynx, the

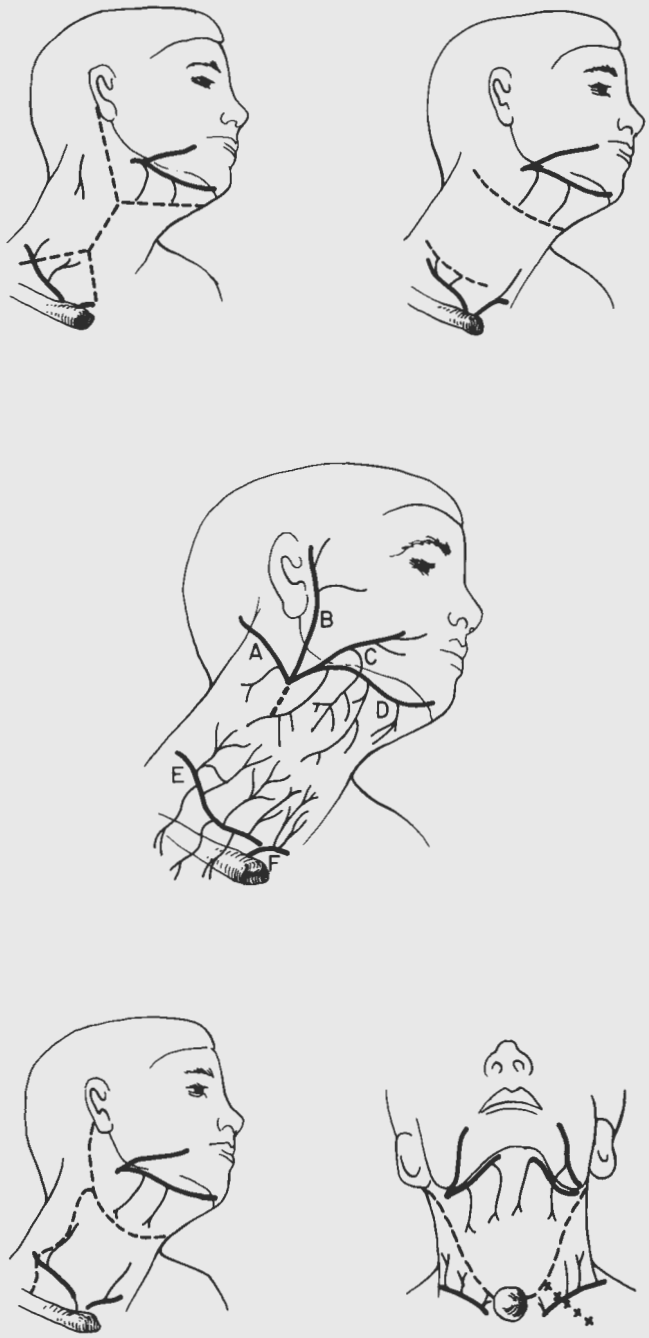

Figure 6-39. Simplified schematic of the normal arterial supply to the skin of the neck and the effect of four commonly used incisions. (*Center*) Normal arterial supply to the skin of the neck: A, occipital artery and the descending branch; B, superficial temporal artery; C, facial artery; D, submental branch of facial artery; E, transverse cervical artery; F, subcapsular artery. (*Upper left*) Incision recommended by Martin (1951).[76] (*Upper right*) Incision recommended by MacFee (1960).[72] (*Lower left*) Incision recommended by Cassisi. This is a modification of the incisions recommended by Ogura (1969), Freund (1967), Conley (1966), and Schobinger.[6,46,102] (*Lower right*) Apron flap described by Durante (1905), often employed for laryngectomy and neck dissection.[30] Two trifurcate junctions occur at the tracheostome in an area with a depleted blood supply; as a result, wound infection and necrosis may occur. (Redrawn from Freeland AP, Rogers JH. The vascular supply of the cervical skin with reference to incision planning. Laryngoscope 1975;85:720–721)

veins of the head and neck are *without valves*, and, therefore, venous blood may be readily shunted to an alternate route when a vein is ligated or obstructed.

Venous blood leaves the cranium through the internal jugular veins, the emissary veins, the diploic veins, and the vertebral veins. The internal jugular vein and even the external jugular vein may be preserved in conservative neck dissections, but in the usual radical neck dissection, the internal jugular vein and the external jugular vein are ligated, thereby removing two major escape routes for blood leaving the brain (see Fig. 6-42). The normal vertebral veins are estimated to be adequate to carry the overload created by ligation of both internal jugular veins.[11,47] The vertebral veins and posterior emissary veins communicate with the occipital plexus and represent a major escape route after radical neck dissection.[47] The nape of the neck should be suspended in the postoperative period to prevent occlusion of this venous system by pillows or dressings. The head rests on a pillow or doughnut-shaped prop, and there should be room to place a hand between the neck and the bed (Levine H, personal communication, 1982). Anomalies of the venous system are frequent, however, so the capacity to shunt venous blood from right to left or vice versa may be poor. The confluence of the venous sinuses is particularly important in the rerouting of blood flow. Venous blood from the superior sagittal sinus flows into the right transverse sinus, which is often larger than the left transverse sinus. Blood from the straight sinus flows into the left transverse sinus. The junction of these veins (confluence) may at times be nearly or completely separate and may thus eliminate the major pathway for the shunting of blood from side to side. Rohrbach[117] reported the autopsy findings for a patient who died after a left neck dissection; the patient's right transverse sinus and internal jugular vein were underdeveloped—"the size of a knitting needle," according to Rohrbach. These anomalies may account for the rare reports of acute difficulties that arise after ligation of one internal and one external jugular vein.[134] Carotid angiograms taken with and without compression of the internal jugular vein may be used in special cases to establish the patency of the anastomoses between the right and left venous system.

Ligation of one or both internal and external jugular veins is regularly accompanied by an immediate rise in the CSF pressure. The rise in pressure is due to the accumulation of intracranial venous blood, which displaces the CSF into the spinal canal. The CSF pressure regularly returns to normal a short time after the ligation of one internal jugular vein; however, after a second jugular vein has been ligated, the pressure may remain elevated unless CSF is removed.

Failure of the venous-lymphatic system to compensate produces a clinical picture of lymphedema of the facial structures, especially of the eyelids; cyanosis; and other signs and symptoms consistent with a sudden increase in intracranial pressure. Patients prefer to sleep with the head elevated, which assists venous drainage.

Fascial Compartments of the Neck

The superficial, middle, and deep layers of the deep cervical fascia form the compartments of the neck. The lymphatic-bearing tissues of the neck are separated from the muscles, nerves, and vessels by this system (Fig. 6-43).[16] Lymph nodes are not present within the carotid sheath or within the muscular sheaths. Therefore, a com-

Figure 6-40.

Figure 6-41. Single-limb incision.

plete removal of the lymphatic tissues may be achieved while preserving the sternocleidomastoid muscle, the jugular vein, and the spinal accessory nerve (functional neck dissection). This is achieved by dissecting the fascia off of these structures. In the event that extensive extranodal spread of tumor or fixation has occurred, one or all of these structures may require resection (radical neck dissection). Bocca and Pignataro[16] provide a detailed discussion of the fascial compartments of the neck.

Indications for Biopsy of Cervical Lymph Nodes

In rare situations, open biopsy of the neck mass must be done before neck dissection. Most initially unknown primary tumors may be detected by thorough head and neck examination, imaging studies, and panendoscopy with directed mucosal biopsy. In the unusual situation that the primary tumor cannot be found, needle biopsy of the neck mass is indicated. Only if the needle biopsy is nondiagnostic should open biopsy be considered. An excisional biopsy is preferable to incisional biopsy when possible. Incisions should be placed in the line of an appropriate neck dissection incision. In the presence of multiple nodes with no primary lesion discovered, an immediate neck dissection makes the most sense because a neck dissection would be required after radiation therapy anyway. In the case of a single node, irradiation after excision of the node offers a cure rate equal to that of a neck dissection plus irradiation and is the recommended plan. Proper work-up of the patient with a neck mass makes open node biopsy an uncommon scenario (see Chap. 15).

◄ **Figure 6-40.** A 43-year-old woman presented with a left neck mass that had enlarged over the previous year. A primary lesion of the left base of the tongue was discovered; biopsy revealed anaplastic squamous cell carcinoma. The lesion extended from the midline of the tongue to the glossotonsillar sulcus and onto the lower pole of the tonsillar fossa. There was a fairly discrete mobile mass, 6 × 3 cm, in the left jugulodigastric area (T3N3A; stage IV). (*A*) The patient had received 1800 cGy through parallel opposed rectangular portals before consultation. Note borderline coverage of the base of the tongue and the upper jugular chain, junctional, and spinal accessory lymph nodes. The lower jugular chain was not included. The entire larynx was in the treatment portal. (*B*) Revised ^{60}Co portals. Note difference in portal borders compared with *A*. The superior margin is 2 cm higher to ensure adequate coverage of the base of the tongue and the junctional lymph nodes. The lower neck received 5000 cGy, through a separate anterior portal to avoid unnecessary irradiation of the larynx, hypopharynx, and spinal cord; the junction between the upper and lower portals falls across the 6-cm lymph node (*dashed line*). (*C*) Portal reduction at 5000 cGy. The spinal cord was excluded from the upper portal, and the superior and anterior margins were reduced 1 cm. Through a reduced anterior portal (*arrow*), 1000 cGy was added to the lower portion of the metastatic lymph node. (*D*) Roentgenogram of treatment portal shown in *B*. Dashed lines represent reduced portal adopted at 5000 cGy. Treatment was completed through parallel opposed fields, ^{60}Co, 6500 cGy tumor dose over 7 weeks; 1000 cGy was added to the base of tongue through a submental boost. The final tongue dose was estimated at 7500 cGy. The maximum dose to the left neck node was 7000 to 7500 cGy; the minimum dose was 6000 cGy. The patient had a left radical neck dissection 4 weeks after radiation therapy. The specimen was negative for tumor. Her postoperative course was uneventful, and she was discharged from the hospital in 1 week. (*E*) Appearance of neck 7½ years after treatment. The solid line represents the carotid artery. The dashed line represents the scar of the radical neck dissection. Note the relationship of the posterior limb in the incision and the trifurcate junction to the artery. The upper portion of the posterior flap lies on the posterior edge of the irradiation portal and received little or no irradiation. The lower portion of the posterior flap received approximately 4000 cGy.

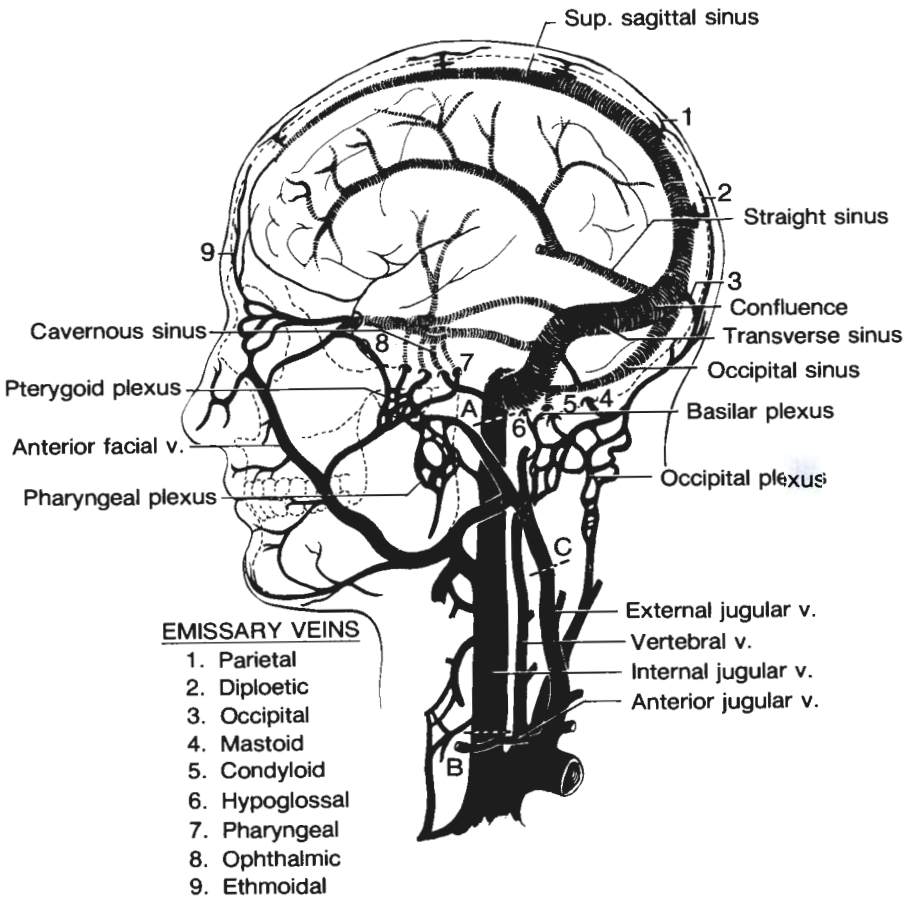

Figure 6-42. Head and neck venous system. (A and B) The usual sites for ligation of the internal jugular vein during a neck dissection. (C) The location for ligation of the external jugular vein. (Redrawn from Eycleshmyer AC, Jones T, eds. Hand-atlas of clinical anatomy. Philadelphia, Lea & Febiger, 1925:53)

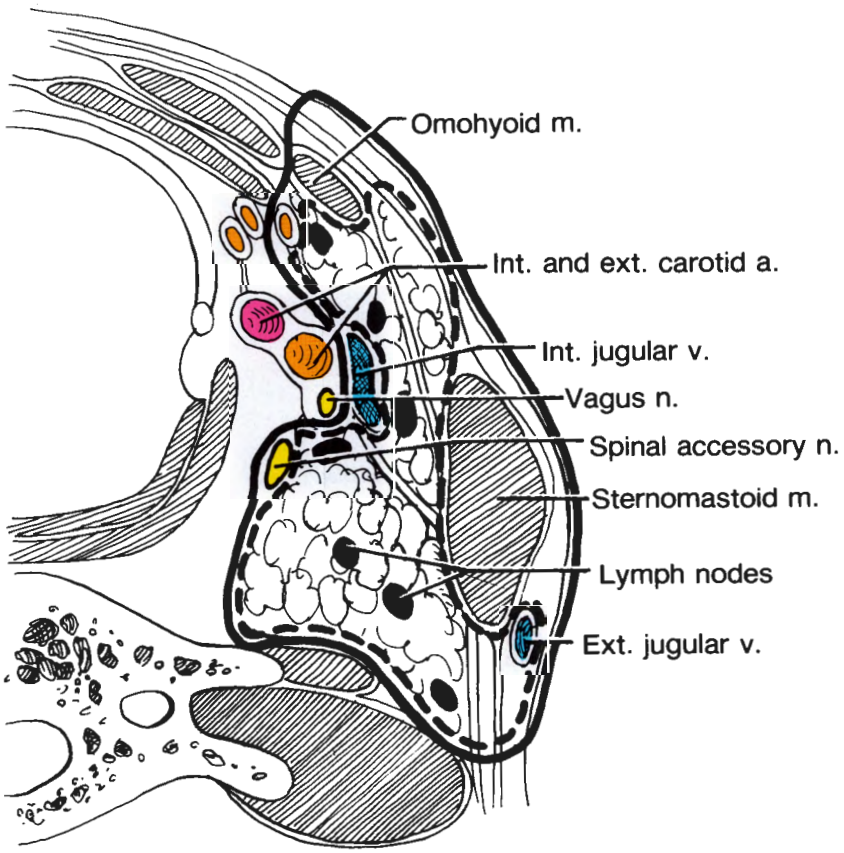

Figure 6-43. Comparison of radical neck dissection and conservative neck dissection. The solid line indicates the structures usually removed with a radical neck dissection, and the dashed line indicates the limits of the conservative neck dissection. (Redrawn from Bocca E, Pignataro O. A conservative technique in radical neck dissection. Ann Otol Rhinol Laryngol 1967;76:976)

Indications and Contraindications for Neck Dissection

In early years, the indications for radical neck dissection were tightly restricted to favorable situations. In 1940, Duffy[29] indicated that the primary lesion must be controlled, limited to one side of the oral cavity, and well differentiated; that the enlarged cervical metastases must be limited to one or two contiguous groups, with no perforation of the lymph node capsule and no contralateral metastases; that there must be no distant metastases; and that the patient must be in good general condition. By 1951, Martin[76] had reduced the number of contraindications and indicated that neck dissection should be done when (1) there was clinical evidence of cancer in the cervical lymphatics, (2) the primary disease was either controlled or was going to be resected in connection with the neck dissection, (3) there was a reasonable chance of resection of the cervical metastatic tumor, (4) there was no evidence of distant metastases, and (5) surgery was more likely to be successful than radiation therapy.

Absolute Contraindications to Neck Dissection

Intradermal satellite nodules and distant metastases are absolute contraindications to neck dissection.

Relative Contraindications to Neck Dissection

SKIN INVASION. The extension of a tumor through the platysma into the skin is a relative contraindication to lymphadenectomy (see Fig. 6-36). As soon as a tumor enters the valveless dermal lymphatics, spread is erratic, and because the tumor has often extended a considerable distance beyond the obvious skin involvement, it generally cannot be removed by surgery alone. Attempts to treat this type of patient with surgery alone would be no more successful than attempts to treat patients with inflammatory breast cancer by surgery alone. We have treated some patients with limited skin involvement with radiation therapy to control the tumor in the dermal lymphatics, followed by removal of the involved skin at the time of radical neck dissection. The radiation therapy is administered in full therapeutic doses in this situation.

BONE OR PERIOSTEAL INVASION. Large neck masses may become attached to the transverse processes of the cervical spine, the base of the skull, or the mandible. Bone films are usually normal. Neck dissection is still possible in some instances after high-dose radiation therapy. A portion of the mandible, the mastoid tip, or rarely a portion of a transverse process may be removed. The high-dose irradiation reduces the size of the mass, and a pseudocapsule forms, which aids in the dissection. These are not cases for the beginning surgeon, because the potential for a surgical disaster is high.

INVASION OF THE NEUROVASCULAR BUNDLE. Large neck masses attach to the carotid vessels (neurovascular bundle), but they rarely invade the wall to any significant depth. This diagnosis may be suggested preoperatively by the size and location of the mass and the relative immobility of the mass, particularly in the superior–inferior direction. A CT scan with contrast or MRI may be of help in assessing resectability. The external carotid may be sacrificed, but ligation of the common carotid and the internal carotid produces a substantial risk of stroke. If high-dose irradiation (6000 to 8000 cGy) is administered before neck dissection, a fibrous capsule develops around the tumor, and it frequently can be dissected free of the carotid. Alternatively, a segment of the common carotid or the internal carotid may be resected and the vessel may be reunited with a graft, but the risk of stroke is still present.

CLINICALLY POSITIVE LOW NECK DISEASE. Clinically positive nodes in the lower neck (ie, below the thyroid notch) are related to an increased rate of distant metastasis and lower survival, but a curative approach is warranted in many cases.[32] Patients with extensive and fixed supraclavicular neck disease are seldom suitable for curative therapy.

Surgical Options for Neck Dissection

As recently as 10 to 20 years ago, it was considered bad practice to do anything but a full radical neck dissection, but this concept has changed, and the surgeon has a number of modified neck dissections that may be used in various circumstances.

The concept of combining surgery and radiation therapy has helped change the surgeon's options in neck dissection. The M.D. Anderson Hospital group led by Jesse[57] indicated that a regional or partial neck dissection was sufficient surgery after whole neck irradiation in instances where only one or two contiguous neck nodes were clinically involved. The radiation therapy was expected to sterilize subclinical disease in the unresected nodes, and the surgical excision was expected to remove any residual cancer not sterilized by the radiation.*

The various types of neck dissection are outlined in Table 6-28, including the nodes resected and the structures preserved. The lymph node groups are depicted in Figure 6-44.[133]

Radical Neck Dissection

In a standard radical neck dissection, the superficial and deep cervical fascia, with its enclosed ipsilateral lymph nodes, is removed with the sternocleidomastoid muscle, the omohyoid muscle, the internal and external jugular veins, the spinal accessory nerve, and the submandibular gland. The incisions used by the surgeon are, to a large extent, governed by the primary lesion if it is also to be resected.

The main advantages of the full radical neck dissection are the improved anatomic exposure, especially near the base of the skull, and the wider margins of excision. Nodes larger than 2 to 3 cm have often penetrated the nodal capsule, and the sternocleidomastoid and omohyoid muscles may be invaded by the tumor. Removal of the sternocleidomastoid provides better exposure near

* There was considerable misunderstanding about this concept when introduced by Dr. Jesse. Many surgeons considered (and still do) that anything less than a radical neck dissection was doomed to failure. The radiation therapists mistakenly thought that the operation was a simple "lumpectomy" after radiation therapy, rather than a regional node dissection.

TABLE 6-28. Proposed Classification of Neck Dissections

Type of Neck Dissection	Node Levels Dissected	Structures Preserved
Standard radical neck dissection (RND)	I, II, III, IV, V	None
Modified radical neck dissection (MRND)	I, II, III, IV, V	SAN
Modified neck dissection (MND)		
Functional neck dissections (FND)	II, III, IV, V (±I)	SCM, IJV, SAN
Selective neck dissection		
Submental triangle dissection	IA	
Submandibular triangle dissection	IB	
Suprahyoid neck dissection	IA and IB	
Anterior neck dissection	IIA, III, IVA	SCM, IJV, SAN, CP
Posterior neck dissection	IIB, V	SAN (±CP)
Interjugular neck dissection	IIA, III, IVA (bilaterally)	
Supraomohyoid neck dissection	IIA, IIB, III, V (±B)	SCM, IJV, SAN (±CP)
Suboccipital node dissection	IIB and suboccipital tissue	
Paratracheal node dissection		
Retropharyngeal and parapharyngeal node dissection	Nodes from the nasopharynx to the cricoid level	

SCM, sternocleidomastoid muscle; IJV, internal jugular vein; SAN, spinal accessory nerve; CP, cervical plexus.
(Suen JY, Goepfert A. Standardization of neck dissection nomenclature. (Editorial) Head Neck Surg 1987;10:76)

the base of the skull and allows a high ligation of the internal jugular vein and more complete removal of junctional lymph nodes.

Bilateral Radical Neck Dissection

The indications for bilateral radical neck dissection and its timing vary according to the initial management of the primary lesion. We generally do not recommend simultaneous bilateral radical neck dissection, especially in conjunction with resection of the primary lesion, because the risk for serious complications is often greater than the chance for cure. Staged bilateral neck dissection is safer, even though it requires two separate operations. Prolonged facial and CNS edema with a secondary syndrome of inappropriate antidiuretic hormone secretion may occur after bilateral ligation of the lymphatic and venous systems. The venous and lymphatic systems eventually compensate over a period of 1 to 2 years in those fortunate enough to survive (Fig. 6-45). If the primary lesion is to be treated by radiation therapy alone, both sides of the neck are irradiated, followed by staged neck dissections.

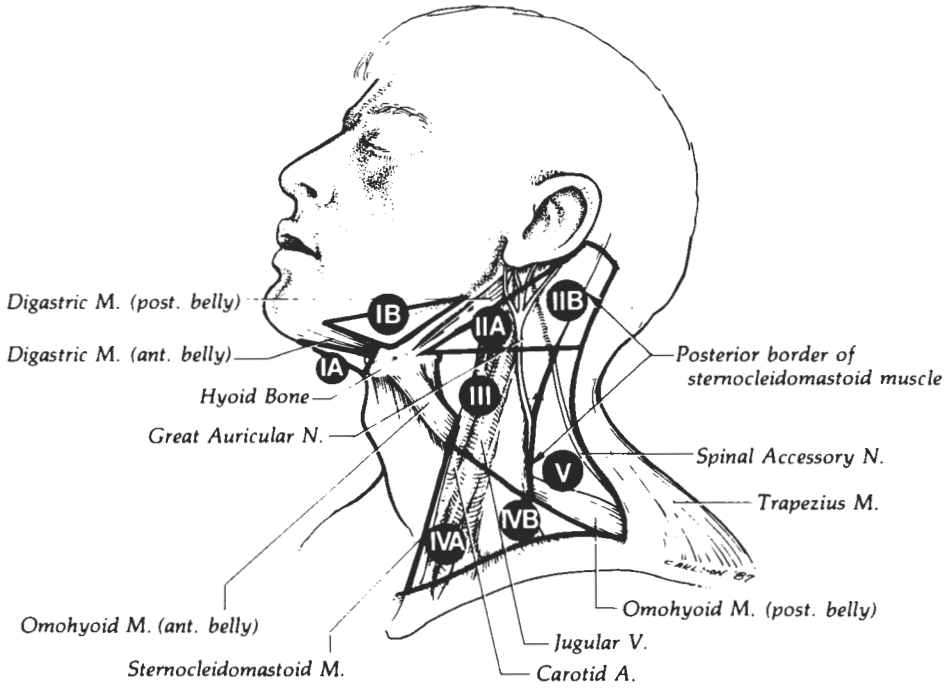

Figure 6-44. Cervical lymph node groups. Roman numerals label the areas referred to in Table 6-28. (Suen JY, Goepfert H. Editorial: standardization of neck dissection nomenclature. Head Neck Surg 1987;10:76)

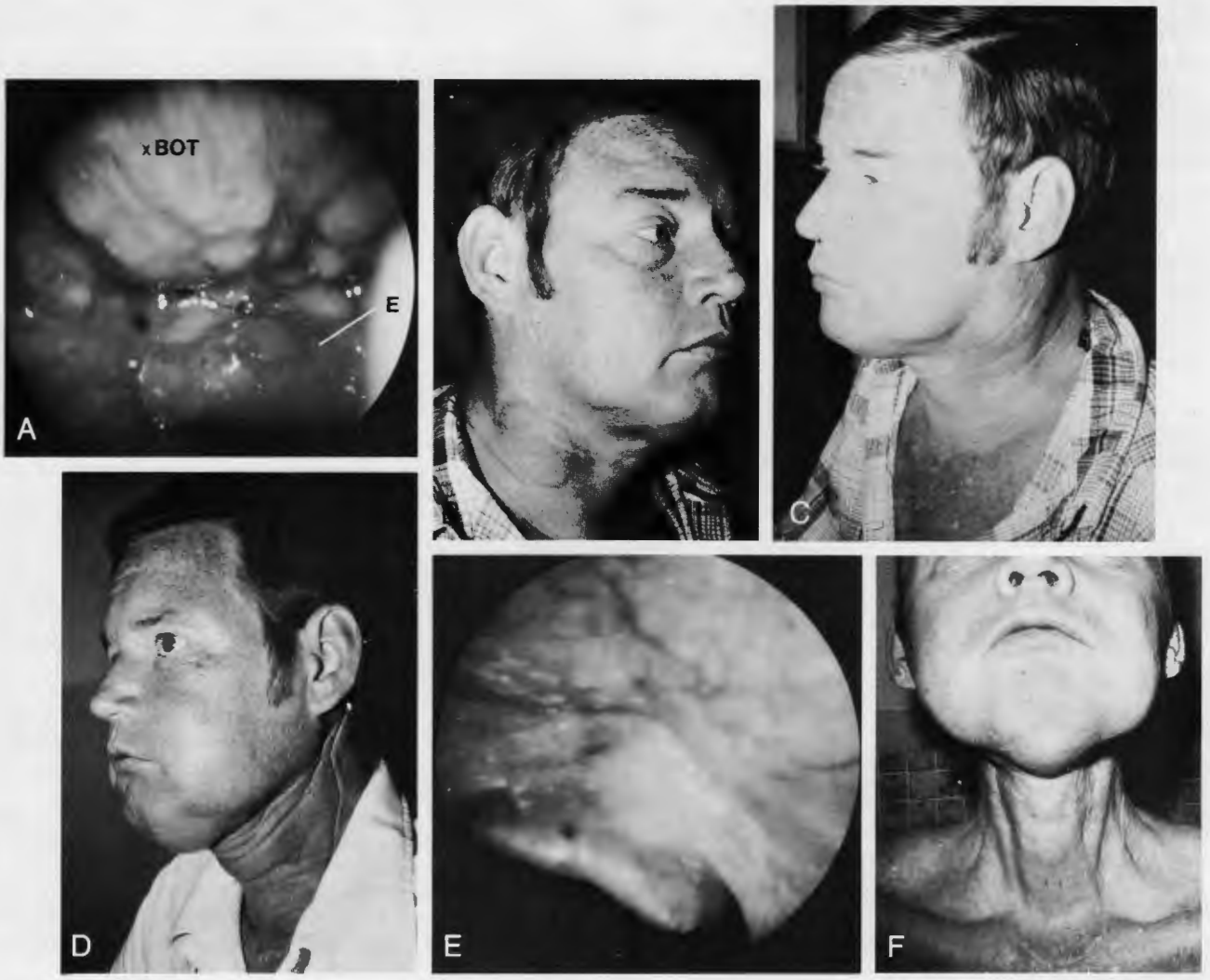

Figure 6-45. A 42-year-old man with squamous cell carcinoma of the base of the tongue and bilateral cervical lymphadenopathy (T3N3B [N2A, N2A]; stage IV). (*A*) Large lesion in the vallecula, extending laterally to both pharyngoepiglottic folds and the lingual surface of the epiglottis and extending anteriorly to the circumvallate papillae (BOT, base of tongue; E, epiglottis). (*B*) Matted modes measuring 3 × 4 cm in the right midjugular region. (*C*) Subdigastric mass measuring 4 × 5 cm in the left neck. The primary and upper neck received a tumor dose of 7400 cGy over 6 weeks, delivered as 120 cGy twice a day. Bilateral electron strips added 1260 cGy to the spinal accessory lymph nodes. Both sides of the lower neck received 6000 cGy over 6 weeks. There was persistent disease in both sides of the neck 1 month after radiation therapy was completed. Simultaneous bilateral modified neck dissections were done by Ogura; both internal jugular veins were spared. The pathology report showed necrotic tumor in large neck nodes. (*D*) Lymphedema 1 month after neck dissection. Edema slowly disappeared over a 2-year period. There were minimal problems with wound healing. (*E*) Two years after the start of treatment, the patient was without evidence of disease at the primary site. (*F* and *G*) Appearance of the neck at 22 months. There was mild lymphedema, which was accentuated by loss of muscle. The patient described a "tight, constricting sensation" in the neck.

The few long-term survivors of radiation therapy and bilateral radical neck dissection complain of difficulty in swallowing, a tight, restrictive sensation in the neck, discomfort in the shoulders, and facial swelling. Although their quality of life is acceptable, these patients have nagging complaints for the rest of their lives.

Modified Radical Neck Dissection Sparing the Spinal Accessory Nerve

Complete severance of the spinal accessory nerve results in atrophy of the trapezius. This is accompanied by shoulder drop and frequent shoulder pain. Function-

ally, the patient has a reduced ability to reach overhead and to lift and carry heavy objects. Physical therapy may reduce the disability to some degree.

In general, the nerve is spared for patients with no clinically enlarged nodes or with small, clinically positive, mobile nodes located away from the base of skull and for patients with clinically positive necks that become clinically negative after radiation therapy. Sparing of the spinal accessory nerve is contraindicated if there are clinically palpable nodes high in the jugular chain, because it interferes with adequate dissection. The decision to save or sacrifice the nerve is often made at the time of neck dissection, and the patient must not be promised that the nerve can be preserved. Careful preservation of the spinal accessory nerve is followed by a temporary and reversible phase of dysfunction of the trapezius muscle with significant recovery occurring by 6 months postoperatively.[114,143] This temporary dysfunction is likely due to traction injury as well as partial devascularization of the nerve. Rarely, the dysfunction is permanent.

The incidence of neck recurrence reported for series in which the spinal accessory nerve was saved is given in Table 6-29.[22,57,120]

Modified Neck Dissections

Modified neck dissections are usually selected for the clinically negative neck or for those with one or two small, mobile, clinically positive lymph nodes.

The posterior cervical group of nodes is the most difficult to resect adequately with any type of modified neck dissection. If the jugulodigastric nodes are pathologically positive or if a positive upper posterior node is discovered, it may be necessary to remove the sternocleidomastoid muscle and internal jugular vein for adequate dissection.

FUNCTIONAL NECK DISSECTION. The functional neck dissection removes only the superficial and deep cervical fascia along with its enclosed nodes, leaving intact the sternocleidomastoid and omohyoid muscles, the internal jugular vein, and the spinal accessory nerve (see Fig. 6-43). Bocca and Pignataro[16] reported no higher incidence of neck failure with this procedure, even in clinically positive necks, than with a standard radical neck dissection.

The functional neck dissection is used if there are no clinically positive nodes in the neck or if there are only small, clinically positive, mobile nodes. Bilateral functional neck dissection may be done for midline lesions.

TABLE 6-29. Neck Recurrence Reported for Series in Which the Spinal Accessory Nerve Was Saved

Institution	Patients With Nerve Saved (%)	Neck Recurrence*
Indianapolis[70]	22	7/98 (7%)
Mayo Clinic[120]	36	7/89 (8%)
Karolinsko[22]	64	7/80 (9%)
M.D. Anderson[57]	66	21/205 (10%)

* Patients with recurrence/patients treated.

One of the major advantages of the functional neck dissection is the preservation of the sternocleidomastoid muscle, which provides coverage of the carotid vessels in the event of a wound necrosis. One half to one third of the sternocleidomastoid muscle mass is lost as a result of reduced blood supply, but the muscle continues to function if the spinal accessory nerve is preserved. Although the internal jugular vein may be spared, it may be sacrificed on one side with almost no risk; in fact, sacrificing it makes the operation a bit easier. If bilateral simultaneous functional neck dissection is planned, the first internal jugular vein should be spared, if possible, in case it must be ligated on the second side.

The disadvantages of the functional neck dissection are that access to the junctional lymph nodes is poorer and the operating time is about 30 minutes longer compared with the radical neck dissection.

SUPRAOMOHYOID NECK DISSECTION. The supraomohyoid neck dissection is a modified regional neck dissection in which the jugular chain lymph nodes above the omohyoid muscle, the upper spinal accessory lymph nodes, the submandibular gland with its prevascular and postvascular nodes, and often the submental lymph nodes are removed. The posterior triangle nodes are not included. The sternocleidomastoid muscle, internal jugular vein, cranial nerve XI, and usually the cervical plexus are spared.

The supraomohyoid neck dissection may be used when a small primary lesion of the oral cavity is to be excised and the neck is clinically negative. If the nodes are found to be positive at the time of the operation, the dissection is extended to a full neck dissection.

Bilateral supraomohyoid neck dissection may be performed in patients with bilateral upper neck disease (Fig. 6-46). Both dissections may be done simultaneously if one internal jugular vein can be preserved. Fewer complications occur, however, if the second neck dissection is carried out 4 to 6 weeks after the initial neck dissection.

The potential for complications is less for a supraomohyoid neck dissection than for a complete functional neck dissection. A supraomohyoid neck dissection does not include the posterior triangle, because of the low incidence of positive nodes in this area with a clinically negative neck. This requires less dissection of the spinal accessory nerve and possibly decreases the incidence of postoperative shoulder weakness. In addition, some of the posterior branches of the cervical rootlets may be saved, preserving posterior cutaneous sensation. A complete neck dissection requires the elevation of more posterior cervical skin, which increases the risk of seroma formation.

The greatest risk involved with supraomohyoid neck dissection is the failure to remove all involved lymphatic tissue. Because the additional morbidity of a complete functional neck dissection is minimal, it is our policy to use a complete dissection rather than a supraomohyoid dissection.

POSTEROLATERAL NECK DISSECTION. The posterolateral neck dissection is used to electively resect lymph nodes associated with skin malignancies (melanomas and squamous cell carcinomas) that arise from the posterior scalp, occiput, and nape of the neck.[48] The regional lymph nodes at risk include the retroauricular, suboccipital, and spinal accessory nodes. The retroauricular nodes lie in the soft tissues, either on or just behind

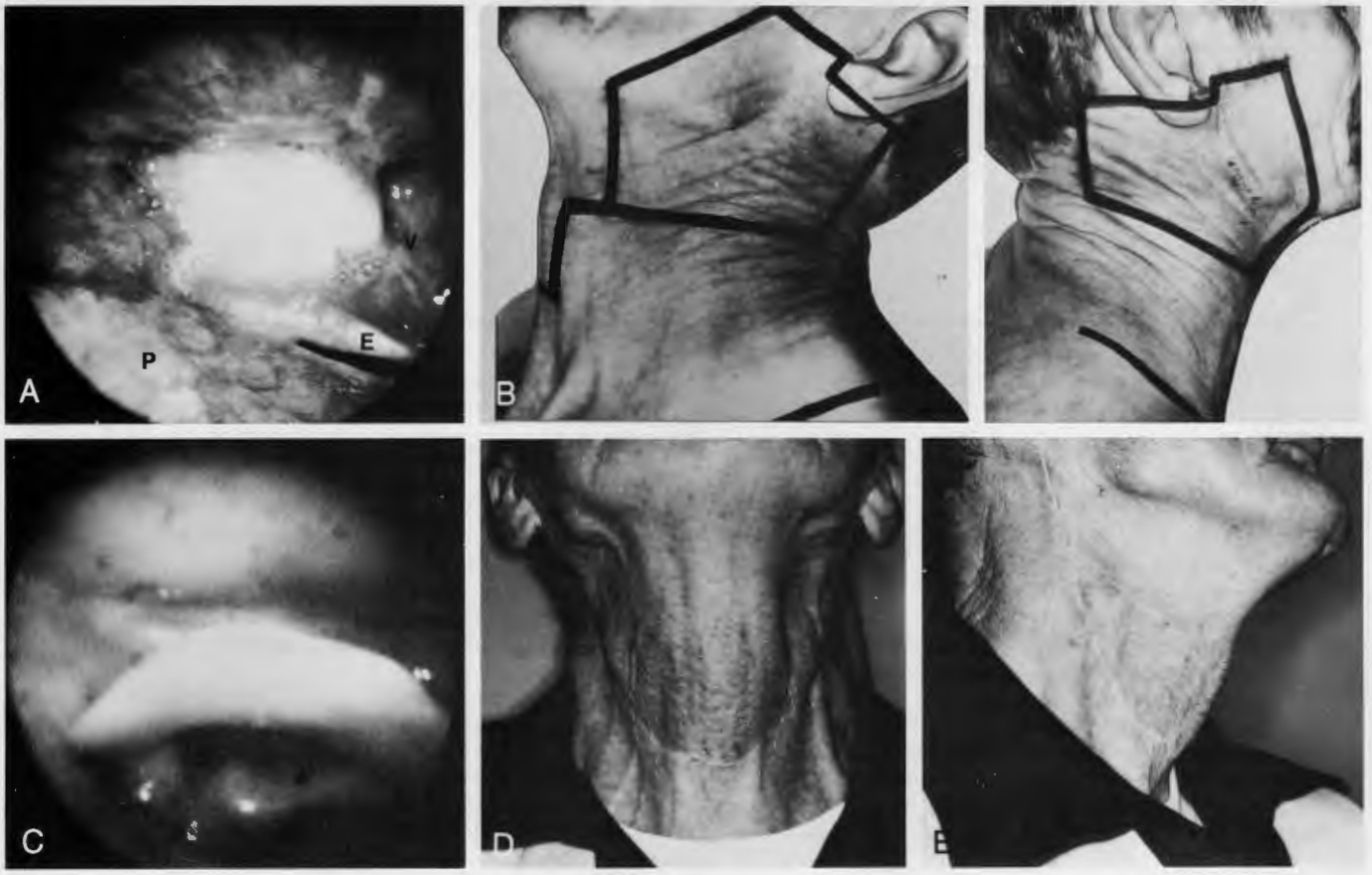

Figure 6-46. A 54-year-old man with poorly differentiated squamous cell carcinoma of the base of the tongue and the vallecula with extension to the epiglottis and left pharyngoepiglottic fold. There was a 3-cm jugulodigastric node on the right and a 4-cm jugulodigastric node on the left (T3N3B). He received a tumor dose of 6000 cGy over 7 weeks, through parallel opposed fields, ^{60}Co, followed by a 1000-cGy submental boost to the primary lesion. The lower neck received 5000 cGy. There was complete disappearance of the primary lesion after 2000 cGy; the nodes were 50% smaller at the completion of treatment. Six weeks later, the patient underwent bilateral supraomohyoid neck dissection. There was no tumor in the nine left neck nodes and seven right neck nodes. There were suspicious nodes located on the left spinal accessory nerve, and the nerve was sacrificed. A large lymph node was found in the right midjugular area, and about 1 cm of the sternocleidomastoid muscle was resected; the right spinal accessory nerve was spared. The patient had an uneventful postoperative course and was discharged 7 days later. He had no significant edema and was free of disease 4½ years after the start of treatment. (*A*) Before treatment (P, posterior pharyngeal wall; E, epiglottis; V, right vallecula. (*B*) Treatment portals. (*C*) Primary site 3 years after the start of treatment. (*D* and *E*) Appearance of the neck 3 years after treatment. Note the preservation of sternocleidomastoid muscles and freedom from significant edema or fibrosis. About one third to one half of the sternocleidomastoid muscle mass is lost; the motor nerve to the sternocledíomastoid muscle is the spinal accessory nerve, wihch was preserved on the right but sacrificed on the left.

the mastoid. The suboccipital nodes are divided into three subgroups: (1) the superficial occipital nodes, which are closely related to the cutaneous branch of the occipital artery and the greater occipital nerve at the insertion of the trapezius to the inferior nuchal line; (2) the deep occipital nodes, which lie underneath the superficial layer of the deep cervical fascia next to the splenius capitis; and (3) one lymph node usually located along the splenius portion of the occipital artery. The occipital and retroauricular nodes drain to the spinal accessory chain and sometimes to the internal jugular chain. If the primary lesion is located on the scalp close to the ear, the lymph nodes in the parotid area are also at risk. A complete regional node dissection for such lesions would include not only a posterolateral neck dissection but also the removal of the lymph nodes of the parotid area and a conventional neck dissection to remove the lymph nodes of the internal jugular chain.

If the primary lesion is present and lies close to the neck dissection limits, it may be incorporated into the neck dissection specimen. Skin flaps are elevated from the posterior edge of the sternocleidomastoid to the posterior midline. The trapezius is separated from the nuchal line and resected down to the level of C3 to C4. The lymph nodes are removed along with the occipital artery. The spinal accessory nerve may or may not be pre-

TABLE 6-30. Regional Recurrence Rates* After Modified Neck Dissection With or Without Radiation Therapy

Sites	Patients With Modified Dissection	Sides With Modified Dissection†	Receiving Radiation Therapy (%)	Neck Recurrences at 2 Years	
				Sides	Recurrences
Oral cavity	448	553 (105)	33	364	37 (10.2%)
Oropharynx	142	181 (39)	55	90	8 (8.9%)
Larynx	265	474 (209)	52	385	18 (4.7%)
Hypopharynx	112	164 (52)	68	96	5 (5.2%)
Total	967	1372 (405)		935	68 (7.3%)

* Recurrence in the neck with primary controlled at 2 years.

† Bilateral modified dissections in parentheses.

(Modified from Byers RM. Modified neck dissection: a study of 967 cases from 1970 to 1980. Am J Surg 1985;150:418)

served, depending on whether the lymph nodes are clinically negative or positive. The spinal accessory nerve forms the inferior limits of the dissection if the lymph nodes are negative. The nodes of the upper internal jugular vein are dissected by retracting the sternocleidomastoid muscle anteriorly. Whether the sternocleidomastoid should be removed depends on the clinical situation. No major cosmetic or functional deformity is noted other than that commonly associated with spinal accessory nerve loss, even for those patients who undergo bilateral dissection. A high rate of regional control is reported for this procedure, which is used mainly for malignant melanoma of the scalp.[48]

Results of Neck Dissection

Bocca and coworkers[17] reviewed the results of 1500 functional neck dissections performed in 843 patients between 1961 and 1982; 87% of the operations were for laryngeal cancer. Eighty percent were in clinically negative necks and 20% for clinically palpable disease. The recurrence rate for clinically negative necks was 2.38% and for clinically palpable disease was 30.4%. When the neck was clinically negative before surgery, there was no difference in the neck failure rate regardless of whether the specimen was pathologically negative or positive. Bocca and coworkers emphasized that some so-called neck recurrences are actually the result of implantation of tumor from the primary site.

Byers[18] reported the results of 1372 modified neck dissections in 967 patients operated on between 1970 and 1980. Failure in the neck was scored only if the primary site was under control at the time of neck recurrence; failure was scored in either side of the neck regardless of whether it had been dissected (Table 6-30). Nine percent of the dissected necks had preoperative radiotherapy, 38% had postoperative radiotherapy, and the remainder had modified neck dissection alone. Fifty-four percent were staged N0. Forty-two percent of the patients had simultaneous bilateral neck dissections. Twenty percent of N0 necks were pathologically positive. Seventy percent of clinically positive necks were found to be positive pathologically; in the subgroup of patients receiving preoperative radiotherapy, only 52% were pathologically positive.

Extracapsular disease was diagnosed in 72% of specimens containing a node or nodes larger than 3 cm. The recurrence rate with extracapsular extension or multiple positive nodes was 26% after surgery alone and 13% after combined treatment.

The recurrence rate in dissected necks for 234 patients undergoing supraomohyoid neck dissection for either oral cavity or oropharyngeal lesions is shown in Table 6-31.

Twenty-six percent of the neck recurrences after supraomohyoid neck dissection for oral cavity tumors occurred in the undissected area in the lower jugular chain. The incidence of mid or low jugular node involvement as the only manifestation of cervical metastasis from primary lesions in the anterior two thirds of the tongue and floor of the mouth was 7%. The risk for mid and low jugular involvement was 12% when the nodes were pathologically positive in the upper neck.

The recurrence rates for anterior neck dissection (ie, removal of the jugular chain lymph nodes), which is used for primary lesions of the supraglottic larynx or hypopharynx, are shown in Table 6-32; both sides of the neck were often dissected.

The recurrence rates after functional neck dissection for 260 patients are shown in Table 6-33.

Spiro and colleagues[128] reviewed 94 patients who underwent 107 supraomohyoid neck dissections for squamous cell carcinoma of the oral cavity and oropharynx. Of 83 necks that were clinically negative, 26 (31%) had

TABLE 6-31. Supraomohyoid Neck Dissection: Recurrence Rates in Dissected Neck Sides—Primary Oral Cavity and Oropharyngeal Sites at 2-Year Follow-Up (234 Patients)

Pathologic Staging	Supraomohyoid Neck Dissection	
	Surgery Only	Surgery and Postoperative Radiation Therapy
N0	7/130 (5%)	2/24 (8%)
N1	1/10 (10%)	0/8 (0%)
Multiple nodes positive for capsular invasion	5/21 (24%)	6/41 (15%)

(Byers RM. Modified neck dissection: a study of 967 cases from 1970 to 1980. Am J Surg 1985;150:418)

TABLE 6-32. Anterior Neck Dissection: Recurrence Rates in Dissected Neck Sides—Primary Laryngeal and Hypopharyngeal Sites at 2-Year Follow-Up (297 Cases)

	Anterior Neck Dissection	
Pathologic Staging	Surgery Only	Surgery and Postoperative Radiation Therapy
N0	10/130 (8%)	1/126 (1%)
N1	0/4 (0%)	0/17 (0%)
Multiple nodes positive for extracapsular invasion	—	3/20 (15%)

(Byers RM. Modified neck dissection: a study of 967 cases from 1970 to 1980. Am J Surg 1985;150:418)

TABLE 6-33. Functional Neck Dissection: Recurrence Rates in Dissected Neck Sides Versus Type of Modified Neck Dissection in All Primary Sites at 2-Year Follow-Up (260 Cases)

	Functional Neck Dissection	
Pathologic Staging	Surgery Only	Surgery and Postoperative Radiation Therapy
N0	3/124 (2%)	0/21 (0%)
N1	0/31 (0%)	1/14 (7%)
Multiple nodes positive for extracapsular invasion	7/27 (26%)	3/43 (7%)

(Byers RM. Modified neck dissection: a study of 967 cases from 1970 to 1980. Am J Surg 1985;150:418)

positive nodes in the specimen. Of 24 clinically positive necks, 71% contained pathologically involved nodes. Of 64 patients whose specimens were pathologically negative, only three patients (5%) had a recurrence in the dissected side of the neck, and two of those were outside the dissected area. There was a 15% rate of neck recurrence in the 26 patients with a clinically negative neck before surgery and pathologically involved nodes. Of 17 patients whose necks were clinically positive before surgery and histologically positive, 29% had recurrence in the neck.

Additional results for neck dissection are found in pertinent anatomic chapters.

Planned Neck Dissection After Radiation Therapy

A common treatment strategy is to treat a primary lesion for cure with irradiation and to manage the neck with irradiation followed 4 to 6 weeks later by neck dissection. Patients selected for this approach have a primary lesion suitable for cure with irradiation and advanced or unresponsive neck disease or clinically positive neck disease not included in the high-dose treatment volume. This approach avoids the morbidity of surgical resection of the primary lesion while increasing the rate of neck control; only patients who develop a local recurrence have the primary site resected.

A comparison of neck control rates according to N stage was given in Tables 6-17 and 6-18 for management by surgery alone, radiation therapy alone, or combined surgery and radiation therapy.

Mendenhall and associates[83] reviewed 161 patients with squamous cell carcinoma treated with radiation therapy to the primary site and neck followed by a neck dissection(s) for clinically positive neck nodes. Control rates in the neck with initial therapy according to number of positive lymph nodes, maximum nodal diameter, and treatment strategy are shown in Table 6-34. Table 6-

TABLE 6-34. Radiation Therapy Plus Planned Neck Dissection: Initial Control of Disease in Each Side of the Neck for Once-a-Day Fractionation, Continuous or Split-Course Irradiation

		Heminecks Controlled/Heminecks Treated	
Clinically Positive Lymph Nodes in the Neck	Maximum Size (cm)	Irradiation and Neck Dissection* (91 Patients, 100 Heminecks)	Irradiation Alone† (139 Patients, 161 Heminecks)[81]
1	<3	10/11 (91%)	59/64 (92%)
	3–4	17/21 (81%)	15/23 (65%)
	5–6	9/12 (75%)	4/5
≥2	<3	4/4	24/32 (75%)
	3–4	13/17 (76%)	10/22 (45%)
	5–6	11/12 (92%)	5/7
≥1	7–8	11/17 (65%)	0/4
	≥9	3/6	0/4

* One patient salvaged by subsequent treatment.

† Two patients salvaged by subsequent treatment.

(Mendenhall WM, Million RR, Cassisi NJ. Squamaus cell carcinoma of the head and neck treated with radiation therapy: the role of neck dissection for clinically positive neck nodes. Int J Radiat Oncol Biol Phys 1986;12:734)

TABLE 6-35. Radiation Therapy Plus Planned Neck Dissection: Neck Disease Control as a Function of Pathologic Findings in Neck Dissection Specimen (108 Patients; 120 Evaluable Heminecks)*

Size (cm)	Proportion With Positive Specimen	Heminecks Controlled/Heminecks Treated	
		Negative Specimen	Positive Specimen
<3	10/23 (43%)	13/13 (100%)	7/10 (70%)
3–4	22/43 (51%)	20/21 (95%)	14/22 (64%)
5–6	10/27 (37%)	17/17 (100%)	6/10 (60%)
7–8	12/21 (57%)	8/9 (89%)	5/12 (42%)
≤9	4/6 (67%)	2/2 (100%)	1/4 (25%)

* One patient excluded because data unavailable.
(Mendenhall WM, Million RR, Cassisi NJ. Squamous cell carcinoma of the head and neck treated with radiation therapy: the role of neck dissection for clinically positive neck nodes. Int J Radiat Oncol Biol Phys 1986;12:735)

TABLE 6-36. Radiation Therapy Plus Planned Neck Dissection: Control of Disease in the Neck as a Function of Node Mobility (109 Patients; 121 Heminecks)

Size (cm)	Proportion of Fixed Nodes	Heminecks Controlled/Heminecks Treated	
		Mobile or Tethered	Fixed
<3	1/23 (4%)	19/22 (86%)	1/1 (100%)
3–4	4/44 (9%)	33/40 (83%)	2/4 (50%)
5–6	9/27 (33%)	17/18 (94%)	6/9 (67%)
7–8	10/21 (48%)	8/11 (73%)	5/10 (50%)
≥9	3/6	2/3	1/3

(Mendenhall WM, Million RR, Cassisi NJ. Squamous cell carcinoma of the head and neck treated with radiation therapy: the role of neck dissection for clinically positive neck nodes. Int J Radiat Oncol Biol Phys 1986;12:735)

TABLE 6-37. Radiation Therapy Plus Planned Neck Dissection: Incidence of Major Wound Complications as a Function of Maximum Subcutaneous Dose and Interval Between Irradiation and Unilateral Neck Dissection*

Maximum Subcutaneous Dose (cGy)	Complications/ Heminecks Treated	
	≤6 Weeks	>6 Weeks
<6000	2/21 (9.5%)	0/12
≥6000	7/50 (14%)	4/14 (29%)

* Once-a-day fractionation, continuous-course irradiation. One patient excluded who died of sepsis 6 days postoperatively without wound complications.
(Mendenhall WM, Million RR, Cassisi NJ. Squamous cell carcinoma of the head and neck treated with rodiation therapy: the role of neck dissection for clinically positive neck nodes. Int J Radiat Oncol Biol Phys 1986;12:738)

TABLE 6-38. Radiation Therapy Plus Planned Neck Dissection: Hemineck Control as a Function of Maximum Node Dose and Number of Treatment Fractions (57 Patients; 61 Heminecks)*

Node Size (cm)	Maximum Node Dose (cGy)	Dose per Fraction (cGy)	Heminecks Controlled/Heminecks Treated
3–4	<5000	Various	3/5 (60%)
	≥5000	≤200	12/16 (75%)
	≥5000	>200	9/9 (100%)
5–6	<5000	Various	0/3 (0%)
	≥5000	≤200	9/10 (90%)
	≥5000	>200	5/5 (100%)
7–8	<6000	<200	1/2 (50%)
	≥6400	<200	3/6 (50%)
	≥6400	≥200	5/5 (100%)

* Continuous-course irradiation, once-a-day fractionation.
(Mendenhall WM, Million RR, Cassisi NJ. Squamous cell carcinoma of the head and neck treated with radiotion therapy: the role of neck dissection for clinically positive neck nodes. Int J Radiat Oncol Biol Phys 1986;12:737)

TABLE 6-39. Radiation Therapy Plus Planned Neck Dissection: Postoperative Complications for Unilateral Neck Dissection (143 Patients)

Complication	Complications	Second Operations	Death
Salivary fistula	1	0	0
Wound breakdown	23	15	0
Bleeding	2	1	1
Pneumonia	2	0	1
Orocutaneous fistula	1	1	0
Lymphatic fistula	2	0	0
Pulmonary embolus	1	0	0
Cardiovascular	2	0	1
Sepsis	1	0	1
Total complications	35*	17	4†
Incidence	33/143 (23%)	17/143 (12%)	4/143 (2.8%)

* 35 complications in 33 patients

† Deaths occurred 6, 7, 8, and 35 days after surgery.

(Mendenhall WM, Million RR, Cassisi NJ. Squamous cell carcinoma of the head and neck treated with radiation therapy: the role of neck dissection for clinically positive neck nodes. Int J Radiat Oncol Biol Phys 1986;12:738)

35 shows that a negative specimen predicts for a high control rate regardless of the initial node size. Nodes judged to be fixed had a much lower control rate than those judged to be mobile or tethered (Table 6-36). There was no difference in neck control rates between those operated on within 6 weeks and more than 6 weeks after irradiation. The operative complications were slightly greater when the neck dissection was done more than 6 weeks after irradiation (Table 6-37). An analysis of neck control rates as a function of maximum preoperative node dose is shown in Table 6-38. There is an increase in control rate as the total dose and dose per fraction increase. The operative complications are listed in Table 6-39. The rate of major wound complications was 6% with a subcutaneous dose of less than 6000 cGy and 17% with a dose of 6000 cGy or more.

Neck Dissection After Twice-a-Day Radiation Therapy

Since 1978, the neck has been managed as discussed in the preceding paragraphs, except that the radiation therapy was 120 cGy twice daily with a 4- to 6-hour interval (see Chap. 12). The dose to the upper and mid jugular areas was in the range of 7440 cGy in 6 weeks to 8160 cGy in 7 weeks; cobalt-60 (^{60}Co) was most often used. None of the patients received chemotherapy. Neck control rates at 5 years are shown in Table 6-40.[107] Almost all patients had a radical neck dissection. Three patients with very advanced disease required pectoralis major flaps for closure of skin defects. None required removal of the carotid artery. Actuarial curves for control of disease in the neck are shown in Figure 6-47 for patients with large solitary masses (N2A and N3A) and in Figure 6-48 for those with multiple neck nodes (N2B and N3B). The addition of neck dissection significantly raised the neck control rate, and this finding is even more significant considering selection of the poorer prognosis cases (ie, those with poor response to radiation therapy or node fixation) for the operation.

The 5-year control rate in 34 N1 necks treated with radiotherapy alone was 91%. Five N1 necks were selected for radiation therapy plus neck dissection, but the disease was controlled in only three. Neck failures after 2 years were uncommon. The time to hospital discharge is shown in Table 6-41.

Four of the 56 patients who underwent planned unilateral neck dissection without flap reconstruction developed wound separations; two closed spontaneously and two required split-thickness skin grafts. Two of the three patients who underwent unilateral neck dissection and pectoralis major flap reconstruction developed necrosis of the flaps, which required deltopectoral flap reconstruction. No carotid ruptures or fatal complications occurred.

TABLE 6-40. Control of Disease in the Neck at 5 Years After Twice-a-Day Irradiation Plus Neck Dissection (56 Patients)*

	Unilateral Neck Dissection	
N Stage	Patients	Control (%)
N1	5	71
N2A	7	86
N2B	16	68
N3A	10	64
N3B†	23	100

* Life-table method.[27]

† Five patients had bilateral neck dissection.

(Parsons JT, Mendenhall WM, Cassisi NJ, Stringer SP, Million RR. Neck dissection after twice-a-day radiotherapy: morbidity and recurrence rates. Head Neck 1989;11:402)

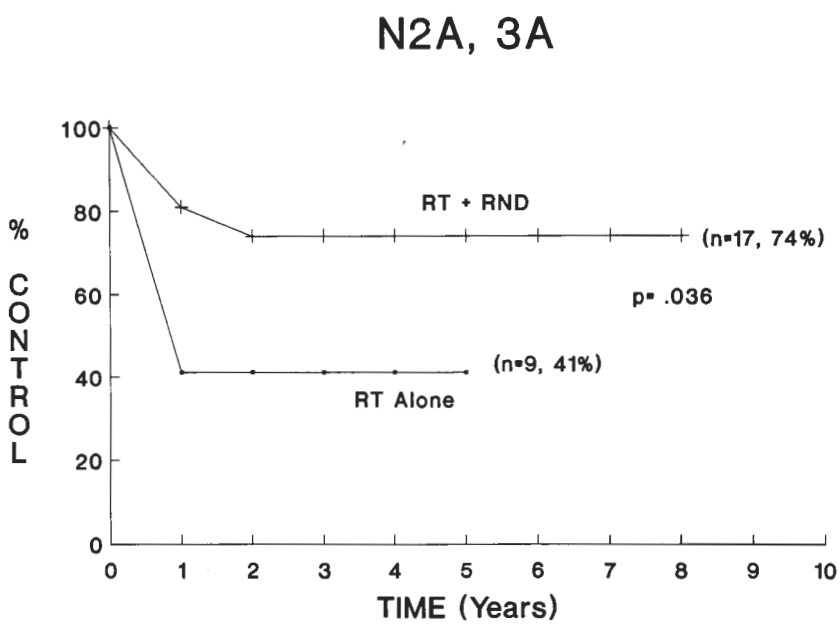

Figure 6-47. Control of disease in the neck (life-table method[27]) with twice-a-day radiation therapy with or without neck dissection for 26 patients with N2A or N3A neck disease, according to treatment technique (RT + RND, irradiation plus neck dissection). Ten of 17 patients (59%) who underwent neck dissection had N3A disease versus 5 of 9 (56%) treated by irradiation alone. (Parsons JT, Mendenhall WM, Cassisi NJ, Stringer SP, Million RR. Neck dissection after twice-a-day radiotherapy: morbidity and recurrence rates. Head Neck 1989;11:402)

Of five patients who underwent planned bilateral radical neck dissections, two patients (one staged, one simultaneous) developed wound separations that led to carotid exposure. Both patients required deltopectoral flap reconstruction. No carotid ruptures or fatal complications occurred.

Complications of Neck Dissection

Factors Affecting Complication Risks

The risk of operative mortality and morbidity is affected primarily by four factors:

Prior irradiation: The total dose of radiation given, the volume of tissues irradiated, the radiation energy (ie, the degree of skin-sparing), and the time elapsed between the irradiation and the operation affect the risk of complications.

Resection of the primary lesion: Neck dissection without resection of the primary site, with or without prior radiotherapy, carries far less risk of a complication than dissection combined with resection of the primary lesion, particularly when the oral cavity or pharynx must be entered.

Tumor extent in the neck: Patients with minimal tumor involvement have fewer complications than those with large masses that require more extensive resection.

The general medical and nutritional status of the patient

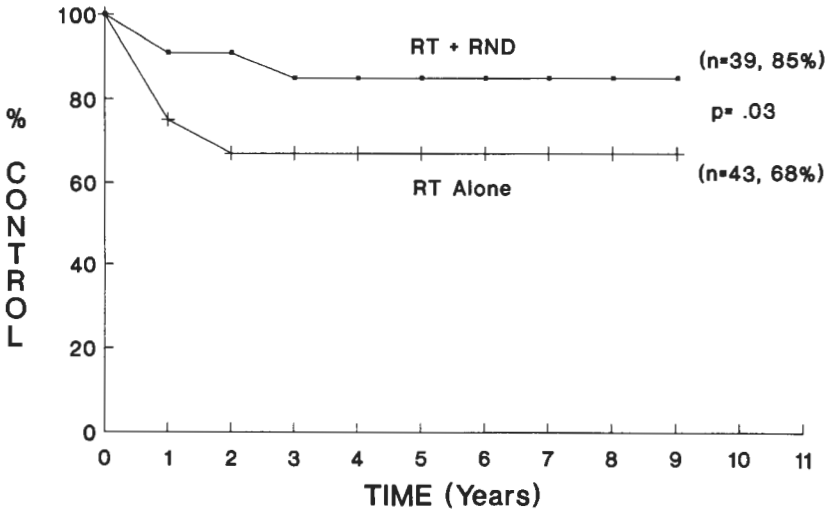

Figure 6-48. Control of disease in the neck (life-table method[27]) with twice-a-day radiation therapy with or without neck dissection for 82 patients with N2B or N3B neck disease, according to treatment technique (RT + RND, irradiation plus neck dissection). Twenty-three of 39 patients (59%) who underwent neck dissection had N3B disease versus 26 of 43 (60%) treated by irradiation alone. (Parsons JT, Mendenhall WM, Cassisi NJ, Stringer SP, Million RR. Neck dissection after twice-a-day radiotherapy: morbidity and recurrence rates. Head Neck 1989;11:403)

TABLE 6-41. Duration of Hospitalization After Unilateral Radical Neck Dissection After Twice-a-Day Irradiation

Institution	Patients	Days Between Neck Dissection and Hospital Discharge		
		Mean	Median	Range
University of Florida or private hospital	29	7	6	3–19
VA Hospital	27	12	9	4–35
TOTAL	56	9	6	3–35

(Parsons JT, Mendenhall WM, Cassisi NJ, Stringer SP, Million RR. Neck dissection after twice-a-day radiotherapy: morbidity and recurrence rates. Head Neck 1989;11:403)

Intraoperative Complications

NERVE COMPLICATIONS. A number of cranial and cervical nerves are at risk to be ligated during the neck dissection. Cranial nerves V through XII, the phrenic and the cervical nerves, the sympathetic plexus, and the brachial plexus have been reported to be injured. The risk is proportionately greater when a large mass involves the nerve or lies near it, in which case the ability to dissect out the mass and preserve the nerve is reduced. The marginal mandibularis branch of the facial nerve may be injured, and the anterior cervical nerves are commonly severed as part of the neck dissection. The incidence of unintentional trauma to nerves is less than 5% and increases with advanced neck disease.

Loss of the spinal accessory nerve may result in atrophy of the trapezius muscle. There is considerable variation in the innervation of the trapezius muscle; sometimes a portion of the innervation comes from the anterior cervical nerves. However, when there is complete atrophy of the trapezius, there is a subsequent shoulder drop, and the patient often complains of shoulder pain. Shoulder drop puts stress on the brachial plexus, and this is aggravated by cold weather or unusual activity.

Even if the spinal accessory nerve is spared, it may not recover function for several months because of the considerable stretching that occurs during the operative procedure. Physical therapy may reduce the side effects of this complication. Younger patients seem to adapt more easily than older patients. If the spinal accessory nerve is removed, a nerve graft, using a portion of the greater auricular nerve, may be used to span the resected portion. However, there may be limited recovery of the function of the trapezius.

Saunders and coworkers[122] reviewed 100 patients to determine the effect of preservation of the spinal accessory nerve after neck dissection. Evaluation of trapezius muscle function after nerve-sparing showed that 53% had normal function, 32% had partial use, and 15% had no function. After nerve sacrifice, 67% had no function and 33% had limited function. Of five patients who had a cable graft, two had normal function and three had partial function. The patients were evaluated for shoulder symptoms such as pain, ache, numbness, tingling, stiffness, or weakness. All patients had weakness of the shoulder; the most common complaint was ache in the shoulder area. In the 55 patients who had preservation of the nerve, 69% were asymptomatic, 29% had mild to moderate symptoms, and 2% had severe symptoms. In the 36 patients in whom the nerve was sacrificed, 50% were free of symptoms. In the patients with a cable graft, 56% had no symptoms and 44% had mild symptoms.

VASCULAR COMPLICATIONS. Air emboli may enter the venous system secondary to a hole in the internal jugular vein. Cancer may involve the carotid sheath, and, during an attempt to literally scrape the tumor off the carotid artery, the vessel wall may be injured. Both of these complications are uncommon. Bilateral ligation of the internal jugular veins may produce increased intracranial pressure, manifested by sudden death, convulsions, eye complications, or nasal hemorrhage. Simultaneous interruption of the lymphatics increases the degree of the symptoms. Cerebrovascular complications may occur from (1) an embolism resulting from an ulcerated carotid plaque, (2) intravascular thrombosis, (3) unintentional ligation of the internal carotid artery, (4) ligation of an external carotid artery with prior internal carotid occlusion, and (5) a transient decrease in cerebrovascular perfusion.[125]

Fisher and coworkers[37] studied the patency rate of the internal jugular vein preserved in a functional neck dissection by using contrast-enhanced CT scan about 2 to 4 weeks postoperatively in 13 patients. Ten veins were patent with a diameter comparable to that on the preoperative CT scan. One vein was narrowed but patent, and two were occluded. At the University of Florida, imaging revealed 23 of 31 veins to be patent after functional neck dissection. After previous radiation therapy, only 6 of 13 veins were patent, and, in the presence of an ipsilateral myocutaneous flap, 3 of 4 veins were occluded. Although it is important to preserve the jugular vein on one side when doing bilateral neck dissections, some surgeons do not attempt to preserve the vein if only one side of the neck is dissected, especially if a myocutaneous flap is used.

LYMPHATIC COMPLICATIONS. A chylous fistula is a serious complication that occurs in about 2% of patients who undergo neck dissection; it is caused by the severing of the thoracic duct or a tributary. Most leaks stop with pressure and a low-fat tube-fed diet. If the chylous drainage persists, it may be necessary to attempt to suture the leak. Chylothorax may occur in some cases.

PULMONARY COMPLICATIONS. Pneumothorax may occur, particularly in operations involving the thyroid and larynx, because the neck dissection often ex-

tends into the upper mediastinum to remove the paratracheal nodes. The pleura at the apex of the mediastinum may inadvertently be torn in this situation; this is a rare complication.

Postoperative Complications

IMMEDIATE COMPLICATIONS. Pneumothorax may not be recognized during the operation because the lung does not collapse until the cuff of the endotracheal tube is deflated. Failure to recognize this complication may result in serious consequences. Development of a hematoma, a seroma, or an infection with resultant necrosis of the wound or flap is the most common immediate postoperative complication. Catheter drainage is used routinely to reduce the risk. Facial lymphedema is commonly seen in the immediate postoperative period, but it begins to regress within a few days if neck dissection is done on only one side. In cases in which a bilateral neck dissection is performed or in which there has been prior radiation therapy, bilateral arytenoid edema is frequent and airway obstruction may occur. Tracheostomy is performed at the time of neck dissection.

DELAYED COMPLICATIONS. Delayed complications include the necrosis of flaps, exposure of the carotid artery, and the potential development of carotid rupture. Although this latter complication is relatively uncommon, it is the most common cause of operative mortality. There may be times when the carotid must be ligated if coverage cannot be obtained and rupture is imminent. The risk of stroke is considerably less when the vessel is ligated electively rather than at the time of rupture.

Laryngeal lymphedema may develop, and, if it is sufficiently severe, a tracheotomy may be required. Lymphedema of the face usually persists to some degree, especially after bilateral neck dissection. This side effect gradually disappears over time. Prior radiation therapy increases the severity and duration of the lymphedema.

Some patients complain of difficulty in swallowing after neck dissection has been performed, even though they have had no radiation therapy or surgical treatment involving the swallowing muscles. The cause is not entirely clear.

Gustatory sweating has been reported after radical neck dissection; the onset was from 1 month to 5 years after surgery.[99] Fracture of the clavicle may occur and is usually precipitated by mechanical stress. Seven cases have been diagnosed at the University of Florida.

Complications of Bilateral Radical Neck Dissection

After bilateral radical neck dissection, the patient's face may appear purple and swollen as a result of venous congestion and the associated lymphedema. The purplish discoloration subsides within a day or two, but the lymphedema persists.

A tall, thin, lanky person usually has fewer complications and side effects from the bilateral operations than a short, obese, "no-neck" patient.

Five cases of blindness after bilateral radical neck dissection have been reported.[74]

Razack and coworkers[113] reported on 61 patients who underwent simultaneous bilateral radical neck dissection; 75% had bilateral clinically positive disease, and 75% had T3 or T4 primary lesions. The operative mortality rate at 30 days was 10%. Seven patients had intraoperative hypotensive episodes, and three died without regaining consciousness. There was an 11% rate of postoperative life-threatening carotid artery hemorrhage. The complications of surgery, many of which were associated with resection of the primary lesion, are listed in Table 6-42. The 3- and 5-year survival rates were 20% and 12%. The same authors also reported on 63 patients who had nonsimultaneous bilateral radical neck dissection; 58% were operated on 6 to 12 months after the first radical neck dissection. The operative mortality rate was 3%. The survival rates at 3 years and 5 years for this group of more favorably staged cases were 60% and 38%, respectively. There were no postoperative deaths when one or both internal jugular veins were preserved.

McGuirt and McCabe[79] compared the complications of a second neck dissection (91 patients) with the complications resulting from a first neck dissection (606 patients). Eleven of the bilateral neck dissections were si-

TABLE 6-42. Postoperative Complications for Simultaneous and Nonsimultaneous Bilateral Radical Neck Dissection

	Patients	
Complication	Simultaneous	Nonsimultaneous
Total number of patients	61 (100%)	63 (100%)
Facial edema and swelling	39 (64%)	19 (30%)
Wound infection	39 (64%)	9 (14%)
Orocutaneous fistula	22 (36%)	4 (6%)
Carotid artery blowout	7 (11%)	0 (0%)
Pulmonary infection	10 (16%)	0 (0%)
Cyanosis	5 (8%)	0 (0%)
Major flap loss	3 (4.9%)	0 (0%)
Unconsciousness	3 (4.9%)	0 (0%)
Mortality	6 (10%)	2 (3.2%)

(Adapted from Razack MS, Baffi R, Sako K. Bilateral radical neck dissection. Cancer 1981;47:199)

TABLE 6-43. Complications of Bilateral Versus Unilateral Neck Dissection

Complications	First Dissection (606 Patients) (%)	Second Dissection* (91 Patients) (%)
Major surgical		
Death	2.8	0.0
Carotid rupture	1.3	1.1
Fistula	19.2†	19.0
Minor surgical (eg, wound necrosis, separation)	25.0	18.7
Flap elevation	5.8	7.7
Other		3.3

* Eleven were simultaneous bilateral dissections.

† Includes only patients who had communications of neck and aerodigestive tract.

(McGuirt WF, McCabe BF. Bilateral radical neck dissections. Arch Otolaryngol 1980;106:428)

multaneous, and 80 were nonsimultaneous (17 were performed within 1 month of the first dissection, and the remainder were done after a longer interval, usually for delayed contralateral metastases). The surgical complications in the two groups are compared in Table 6-43.

Operative Mortality

The mortality rate after ipsilateral neck dissection without resection of the primary lesion and without prior radiation therapy is less than 1%. When the neck dissection is combined with resection of the primary lesion, it takes on the operative mortality for the resection. For bilateral, nonsimultaneous, staged neck dissections, the operative mortality is low, 0% to 3.2%.[79,113] Simultaneous bilateral radical neck dissection was associated with a 10% operative mortality rate in Razack's series.[113]

REGIONAL LYMPH NODE IRRADIATION

Clinically Negative Neck

When the lymph nodes are clinically negative and the risk of subclinical disease is 10% to 15% or greater, the lymph nodes are included and receive a minimum dose equivalent to 4500 cGy over 4½ weeks. In some clinical situations, the first-echelon nodes receive a much higher dose incidental to irradiation of the primary lesion. In the treatment portals used for cancers of the oropharynx, larynx, and hypopharynx, most of the high-risk neck nodes are encompassed by slight enlargement of the portals used to include the primary lesion. For nasopharynx, nasal cavity, paranasal sinus, and most oral cavity lesions, the portals must be extended to include the first-echelon lymph nodes. Treatment techniques must be devised to include the lymph nodes but restrict normal-tissue irradiation to a minimum. The decision to use elective lymph node irradiation depends on several factors:

- Primary site
- Risk for bilateral subclinical disease
- Histologic grade and vascular space invasion
- Depth of invasion and size of the primary lesion
- Difficulty of neck examination
- Relative morbidity for extending the lymph node coverage related to the risk of subclinical disease
- Likelihood that the patient will return for frequent follow-up examinations
- Suitability of the patient for a radical neck dissection should tumor appear in the neck

Examples of portal design for elective irradiation of the neck are shown in Figures 6-49 through 6-54. The lymph nodes at risk vary with each site, and the nodes at risk are specified in the appropriate chapter. The risk for subclinical disease in the lower neck and spinal accessory nodes is admittedly small when the first-echelon nodes in the upper neck are negative. A separate anterior en face lower-neck portal with larynx, pharynx, and spinal cord shielding is used for low neck node irradiation for primary lesions of the oral cavity, nasopharynx, and oropharynx; the junction is usually near the thyroid notch (see Fig. 6-49). For irradiation of supraglottic, hypopharyngeal, and advanced (T3-T4) glottic lesions, the anterior low neck portal is still used, but larynx shielding is not possible, and the junction is determined by the inferior extent of the primary lesion; a small, narrow midline shield is used to avoid overlap of the spinal cord (see Fig. 6-51*B* and 6-53*B*). The lateral paratracheal lymph nodes are at risk in these cases, particularly for lesions with subglottic extension. (For details on elective neck irradiation for nasal cavity, nasal vestibule, and paranasal sinus primary tumors, see Chap. 22.)

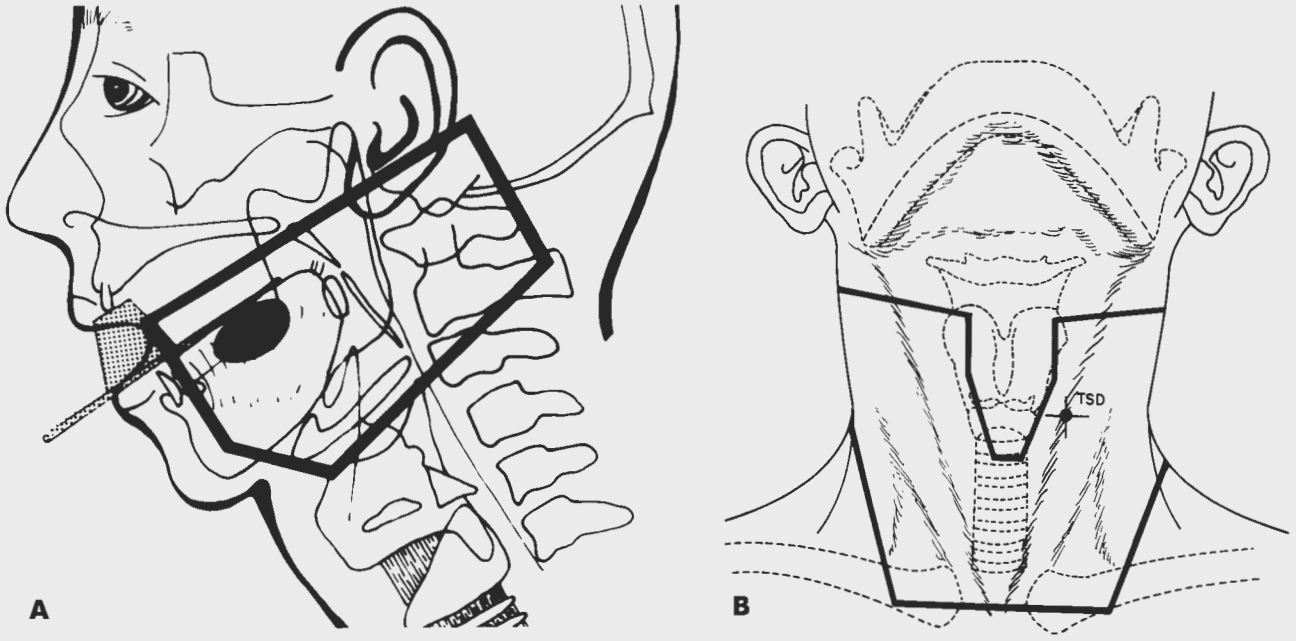

Figure 6-49. (*A*) Example of portal used to irradiate a primary tumor of the oral tongue along with first-echelon clinically negative lymph nodes. The lower border is placed at the level of the thyroid notch. (*B*) A separate low-neck portal is used to irradiate the mid and low jugular nodes.

Clinically Positive Nodes

The treatment plan for the patient with clinically positive lymph nodes depends on the management of the primary lesion; on the size, number, and location of the palpable lymph nodes; and the patient's willingness to accept a neck dissection.

Primary Lesion to Be Managed by Irradiation

If the primary lesion is to be treated by radiation therapy alone, the clinically positive lymph nodes plus the contiguous clinically negative lymph nodes are included. If the contralateral neck is clinically negative, it may also be electively irradiated; an estimation of the contralateral risk must be made for each anatomic site.

The relative control rates with radiation therapy alone versus radiation therapy followed by neck dissection are shown in Table 6-34.[83] (See also Tables 6-17 and 6-18.) The recommendation for neck dissection is based on node size and fixation, multiplicity of nodes, and response of the nodes to radiation therapy.

If neck dissection is to follow radiation therapy, the dose to the nodes varies with size, location, mobility, and response to irradiation. The control rate is related to the radiation dose given before the neck dissection and the

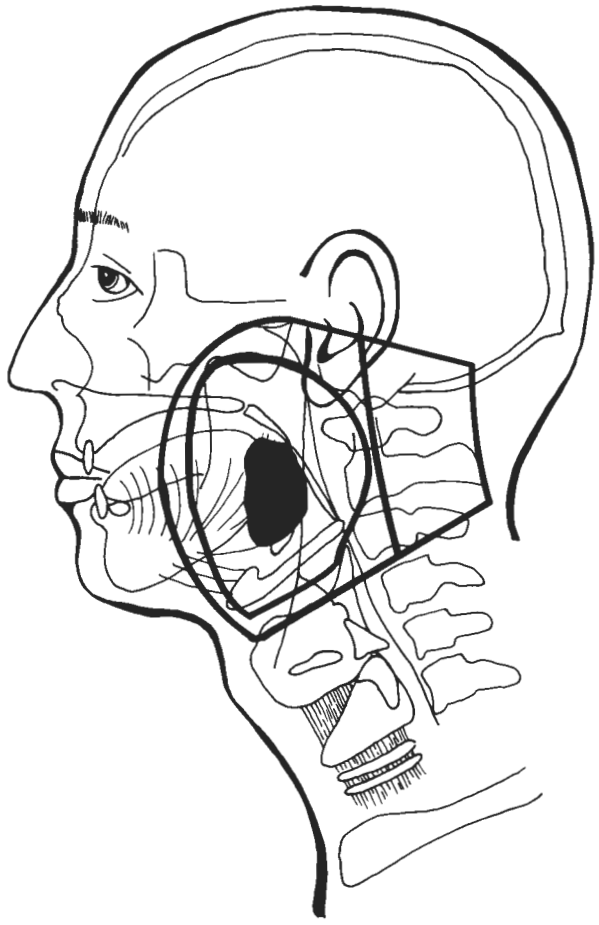

Figure 6-50. Example of portal arrangement for treating the clinically negative neck for a carcinoma of the oropharynx. The superior border is placed about 2 cm above the tip of the mastoid to ensure including the junctional nodes. The lower neck portal would be similar to Figure 6-49*B*. (Parsons JT, Million RR. Treatment of tumors of the oropharynx: radiation therapy. In: Thawley SE, Panje WR, ed. Comprehensive management of head and neck tumors. Philadelphia, WB Saunders, 1987:689)

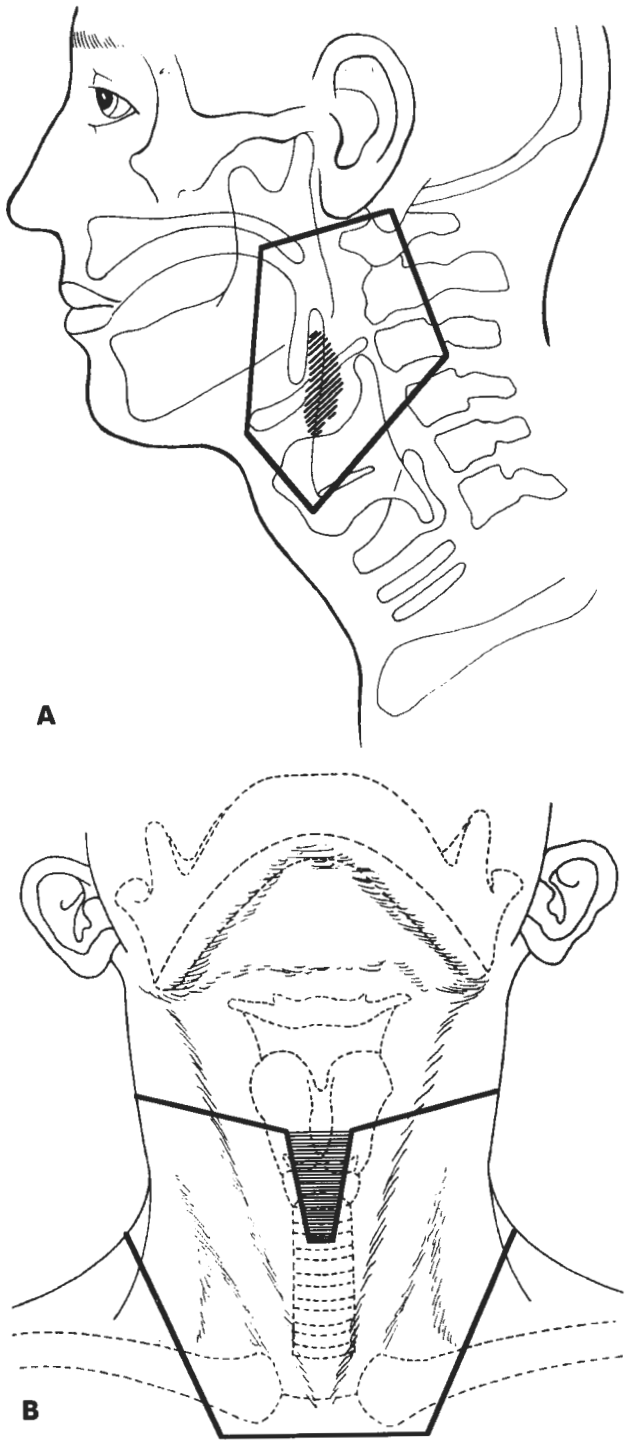

Figure 6-51. Example of portal configuration for a small primary lesion of the upper epiglottis without extensive preepiglottic space involvement and with a clinically negative neck. (*A*) Lateral view. (*B*) Anterior view of lower neck portal.

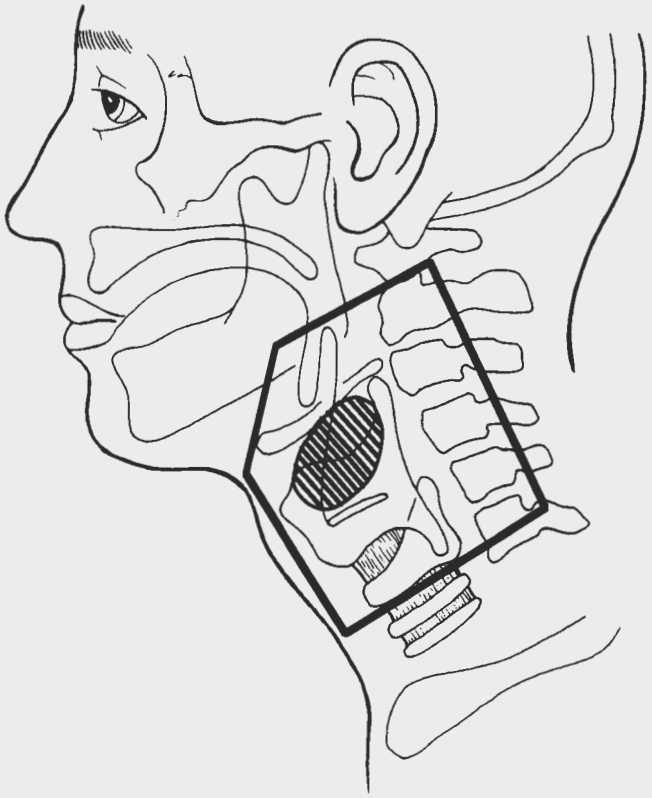

Figure 6-52. Example of portal for lesion of the lower epiglottis or false vocal cord and a clinically negative neck. The subdigastric nodes are included but not the junctional nodes. Depending on the anatomy and tumor extent, the anterior border may fall off (ie, "flash") or a small strip of skin may be shielded. The low neck portal would be similar to Figure 6-51*B*.

diameter of the neck mass, as shown in Table 6-38. A large node mass may be freely mobile, located in the upper neck but judged to be free of the carotid, with a good tumor-free space between the mass and the base of skull, spine, and mandible; large doses are not required in this situation. A large mass in the neck that is seemingly fixed or tethered to the base of skull, skin, or neurovascular bundle gives the surgeon more technical difficulty. Therefore, the final prescribed dose is usually 6000 to 8000 cGy to the mass.

Parallel opposed anterior and posterior portals with wedges are used for the final boost. Large lymph nodes may not show much regression during the course of the radiation treatments, but they often show major change by the time the patient returns in 4 to 6 weeks for neck dissection. The node mass usually develops a thick capsule that facilitates dissection.

If neck dissection is undesirable from a medical standpoint, radiation therapy alone cures a significant number of patients with positive neck nodes (Table 6-44).[81] The control of involved lymph nodes seems to parallel the response and control of the primary lesion. The final dose to the lymph nodes is gauged by their original size (Table 6-45). An interstitial implant may be used in selected cases for a boost dose. The dose for lymphoepitheliomatous nodes may be less if they show rapid, early regression.

Patients with bilateral neck disease require individualized planning with the surgeon. If the neck disease is minimal on one side, irradiation may be used for control on that side, and neck dissection is used on the side that has the major disease. If there is major bilateral neck disease, bilateral neck dissection follows the radiation therapy.

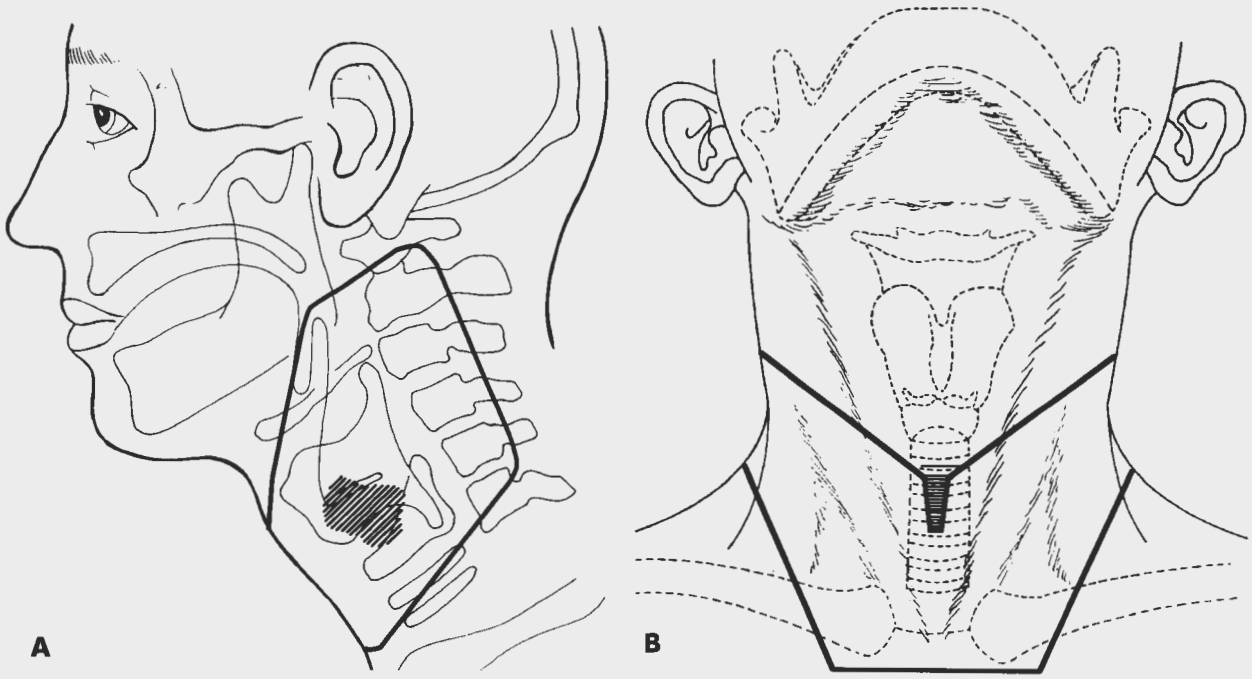

Figure 6-53. Example of a portal for T3N0 glottic carcinoma. (*A*) The subdigastric nodes are included but not the submandibular nor the junctional nodes. It is necessary to irradiate the anterior skin because of anterior commissure disease. (*B*) Low neck portal. The main nodes at risk are the low jugular and lateral paratracheal. The Delphian node would be in the primary portal. A very narrow and short midline shield is used.

TABLE 6-44. Results of Treatment of Positive Neck Lymph Nodes With Irradiation Alone: Lymph Node Control Versus Treatment Technique*

	Controlled/Treated	
Size (cm)	Continuous Course	Split Course
<1.0	5/5	2/2
1.0	29/35 (83%)	19/23 (83%)
1.5–2.0	42/49 (88%)	20/24 (83%)
2.5–3.0	14/19 (74%)	10/18 (56%)
3.5–6.0	14/20 (70%)	10/17 (59%)
≥7.0	0/2	0/5

* Excluded: less than 5000 cGy for nodes up to 1 cm and less than 5500 cGy for nodes 1.5 cm or larger.
Note: University of Florida data; patients treated October 1964 to April 1980; analysis March 1983. (Mendenhall WM, Million RR, Bova FJ. Analysis of time-dose factors in clinically positive neck nodes treated with irradiation alone in squamous cell carcinoma of the head and neck. Int J Radiat Oncol Biol Phys 1984;10:640)

Primary Lesion to Be Managed by Surgery

If the primary tumor is to be managed by an operation, a neck dissection is done and postoperative irradiation is added as needed. If the neck nodes are considered unresectable, preoperative irradiation is used with a boost dose given to the major mass, as outlined in the previous section.

General Principles of Irradiation Techniques for the Cervical Lymphatics

Except for lesions of the nasal cavity and the paranasal sinuses, the first-echelon lymph nodes are included in the treatment portals along with the primary lesion.

Typical treatment portals were shown in Figures 6-49 through 6-54 and are also in specific anatomic chapters. Design of the neck portion of the portal should be carefully planned to avoid as much normal tissue as possible. It is possible to avoid flashing of the anterior midline submental skin in most situations; exceptions are primary lesions of the lower supraglottic larynx and the vocal cords. Sparing of this strip of skin reduces acute skin reactions and subcutaneous fibrosis and helps reduce lymphedema.

The lower neck lymph nodes are electively or therapeutically irradiated initially through a separate anterior portal when possible. The junction between the primary portals and the lower neck portal is generally placed at the thyroid notch for primary lesions of the oral cavity, oropharynx, and nasopharynx (see Figs. 6-49 and 6-50).[108]

Placement of the junction line between the upper and lower neck portals at or near the thyroid notch is an important technical point, because it eliminates or reduces unnecessary irradiation to the larynx, hypopharynx, and spinal cord.[87] Failure to adopt this technique adds greatly to the acute and chronic sequelae. The junction is lower in the neck for primary lesions of the larynx and hypopharynx (see Figs. 6-51 through 6-54).

The junction between the upper and lower neck portals is a common line. It is our practice to irradiate the junction line in the treatment of the upper neck portal and to exclude it in the treatment of the lower neck portal, treating the line only once. Radiation therapists not familiar with this technique are concerned about overtreatment or undertreatment at the junction. Recurrences have not been identified in the clinically negative neck at the site of the junction. Three portals contribute dose to the junction site, including exit dose from the contralateral primary portal. It is nearly impossible to calculate the dose at the junction site; if anything, there is probably a slight overdose rather than an underdose. It is rare to see a strip of moist desquamation or fibrosis at the junction. It makes no sense to irradiate unnecessarily the larynx, hypopharynx, cervical esophagus, and a long length of cervical spinal cord to save a possible minor change in the skin and subcutaneous tissues. The junction line between the upper and lower neck portals is slanted upward (see Figs. 6-49*A* and 6-50*A*) to further exclude small portions of the larynx (arytenoids), phar-

TABLE 6-45. Dose Guidelines for Squamous Cell Carcinoma Metastatic to the Cervical Lymph Nodes

	Dose (cGy)	
Node Size (cm)	1000 cGy/wk	900 cGy/wk
≤1.0	6000	6500
1.5–2.0	6500	7000
2.5–3.0	7000	7500
3.5–6.0	7500	8000

Note: Based on University of Florida data; patients treated October 1964 to April 1980; analysis March 1983 by W. M. Mendenhall, MD.

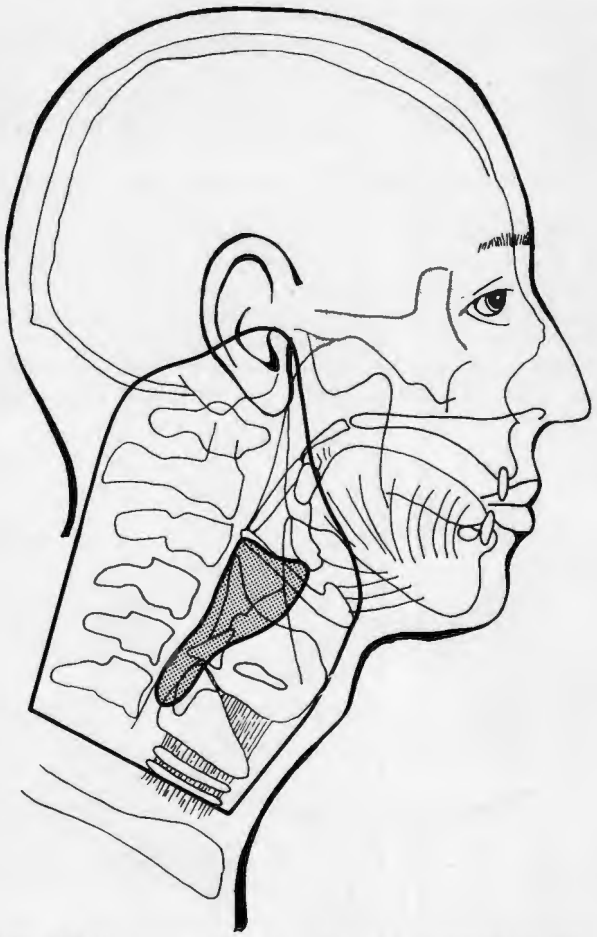

Figure 6-54. Portals used for the initial treatment volume in a patient with carcinoma (*stippled area*) of the pyriform sinus and a clinically negative neck. Superiorly, the portal covers the junctional and retropharyngeal lymph nodes. The submandibular nodes are not included, but the spinal accessory chain is included. Anteriorly, at least 1 cm of skin and subcutaneous tissues (as viewed from the lateral projection) is usually spared. The inferior border is 2 to 3 cm below the bottom of the cricoid cartilage and is slanted to facilitate matching with the low neck portal and to avoid irradiating the shoulders. The posterior field edge usually encompasses the spinous process of the C2 vertebral body. As treatment progresses, portal reductions are made to shield the spinal cord and to limit the volume of mucosa that receives high-dose irradiation. The low neck portal would be similar to Figure 6-53*B*. (Parsons JT, Mendenhall WM, Bova FJ, Million RR. Head and neck cancer. In: Levitt SH, Khan RM, Potish RA, eds. Levitt and Tapley's technological basis of radiation therapy: practical clinical applications, ed 2. Philadelphia, Lea & Febiger, 1992:206)

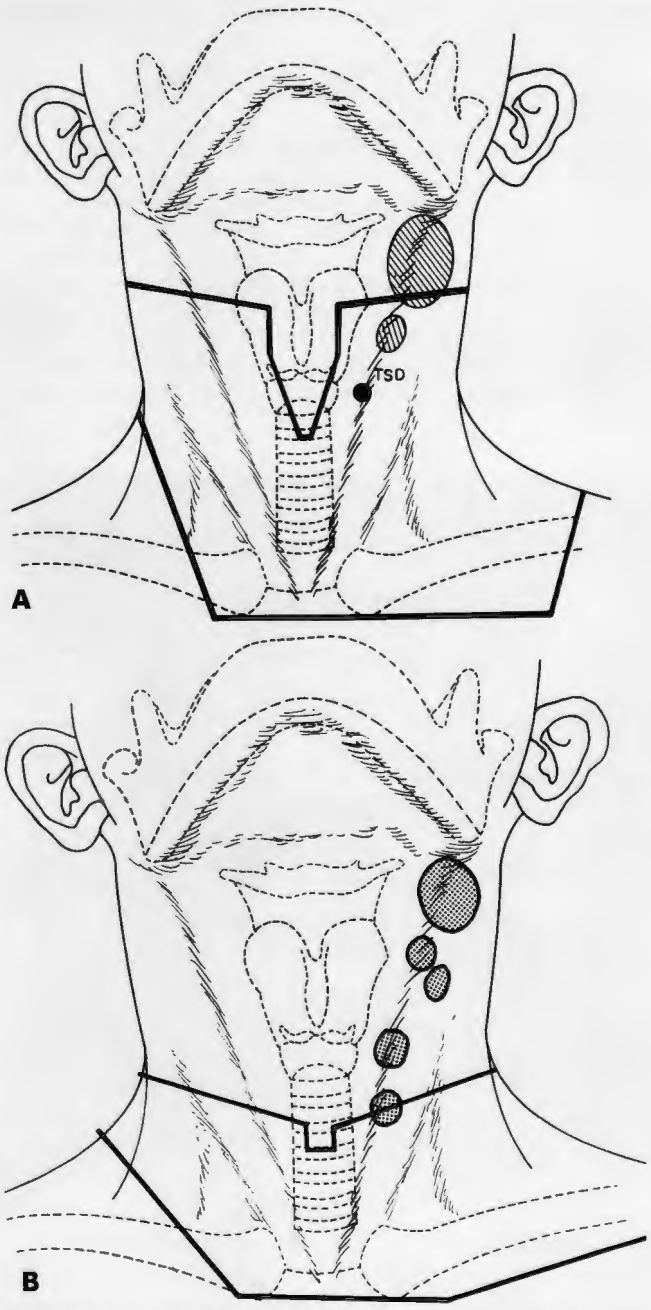

Figure 6-55. Modification of the low-neck portals when the neck is clinically involved. (*B* from Parsons JT, Mendenhall WM, Bova FJ, Million RR. Head and neck cancer. In: Levitt SH, Khan RM, Potish RA, eds. Levitt and Tapley's technological basis of radiation therapy: practical clinical applications, ed 2. Philadelphia, Lea & Febiger, 1992:230)

ynx, and spinal cord. Some therapists have advocated mathematical formulas for calculating a separation between the upper and lower neck portals; we have no experience with this method and see no need for it. One example of a neck failure occurring in the gap has been seen, and the patient died of persistent neck disease. The lower neck portal is collimated by stacking blocks on a shadow tray (hand blocking) rather than by using a shield of Lipowitz's metal. The preferred beam for the low neck treatment is 4 MV or ^{60}Co; 6 MV may underdose superficial neck nodes. The lateral borders in the lower neck portal are placed just around the root of the neck when the upper neck is clinically negative and the risk of disease is small. The lower neck portal is modified when there are enlarged lymph nodes in the neck (Fig. 6-55).[106] The lateral borders are placed at the junction of the clavicle with the trapezius when there is risk for supraclavicular disease, such as with major disease in the upper

neck, in poorly differentiated tumors, or for carcinomas of the nasopharynx.

The larynx shield cannot cover the entire cartilage without producing a low dose in the internal jugular vein lymph nodes that lie adjacent to the most posterolateral margin of the thyroid cartilage. The larynx shield can extend inferiorly, usually to the level of the cricoid or the first two tracheal rings, but the extension must be tapered because the nodes tend to lie closer to the midline in the lower neck. A shield for the larynx and trachea has been fashioned that extends inferiorly over the trachea. However, even this narrow tracheal shield casts a wide shadow and must be precisely placed (Fig. 6-56). It is common to observe a lower neck portal that extends out to the shoulders, encompassing supraclavicular nodes that are not at risk, with a wide midline block that partially shields the high-risk middle jugular nodes and completely shields the lower jugular and paratracheal lymph nodes (Fig. 6-57). The major risk in the low neck portal in a clinically negative neck is in the midjugular nodes.

When clinically positive lymph nodes are present, for any of the primary sites, the neck portals increase proportionally not only to cover the obvious gross disease but also to include contiguous lymph nodes that are at risk. If neck dissection cannot be added, the dose must be raised by additional photon treatment, an appositional electron portal, or an interstitial implant. The concomitant boost technique may be used to raise the weekly node dose to 1200 to 1500 cGy per week. Frequently,

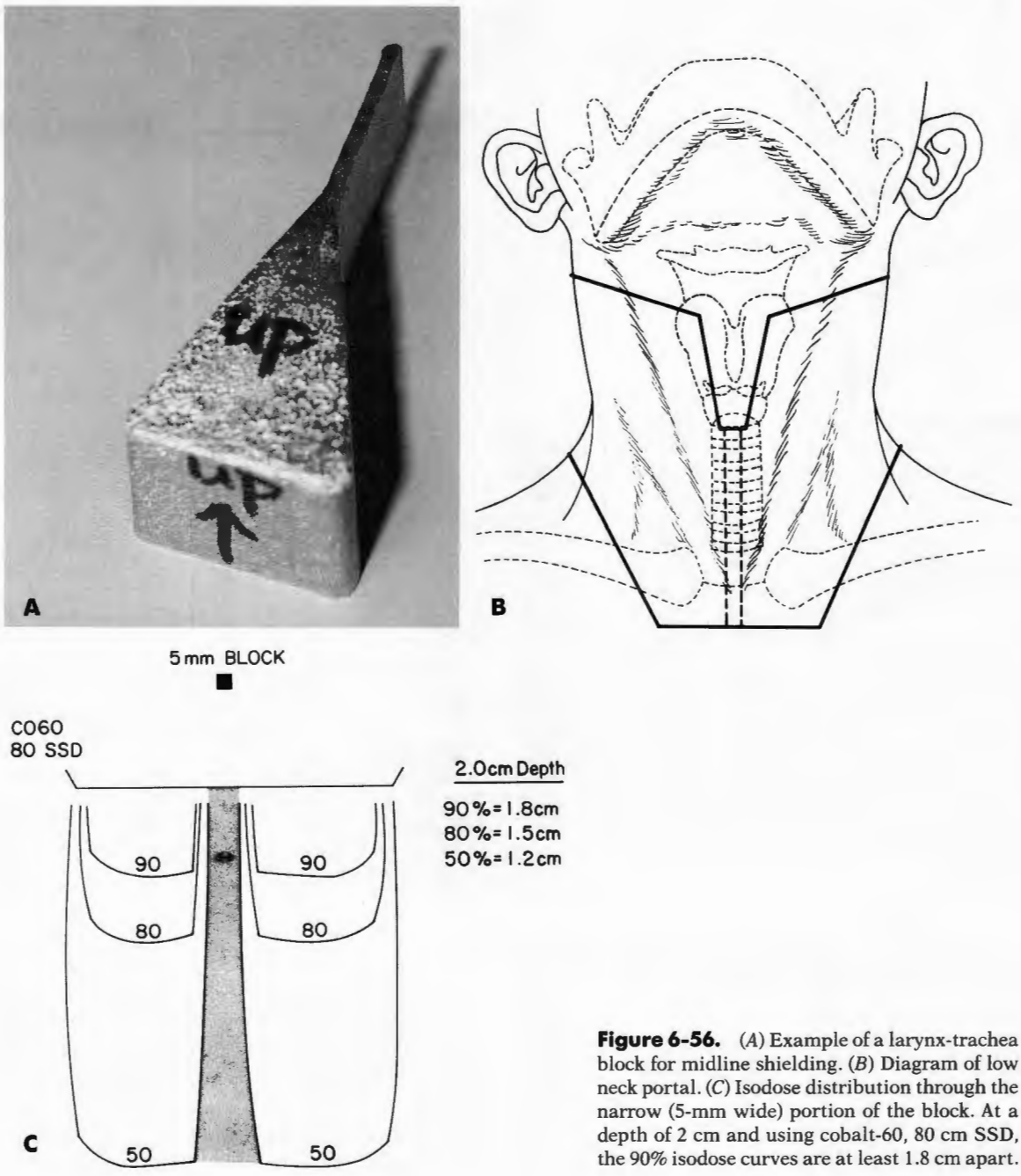

Figure 6-56. (*A*) Example of a larynx-trachea block for midline shielding. (*B*) Diagram of low neck portal. (*C*) Isodose distribution through the narrow (5-mm wide) portion of the block. At a depth of 2 cm and using cobalt-60, 80 cm SSD, the 90% isodose curves are at least 1.8 cm apart.

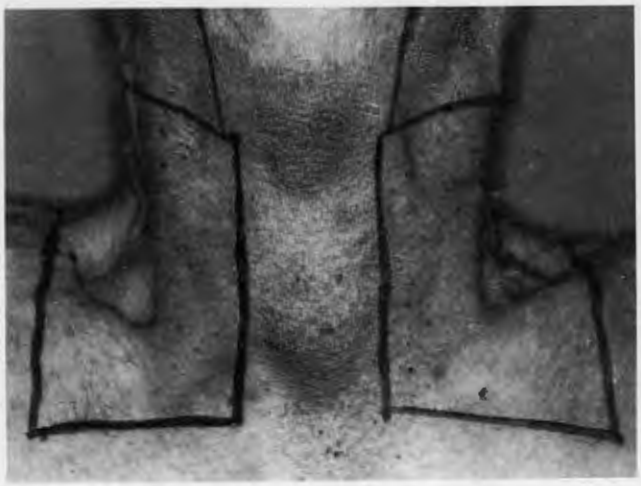

Figure 6-57. INCORRECT design of midline shielding of an anteroposterior low neck portal. The lower jugular lymph nodes are shielded or, at best, in a marginal dose area, and the midjugular nodes are in a marginal dose area.

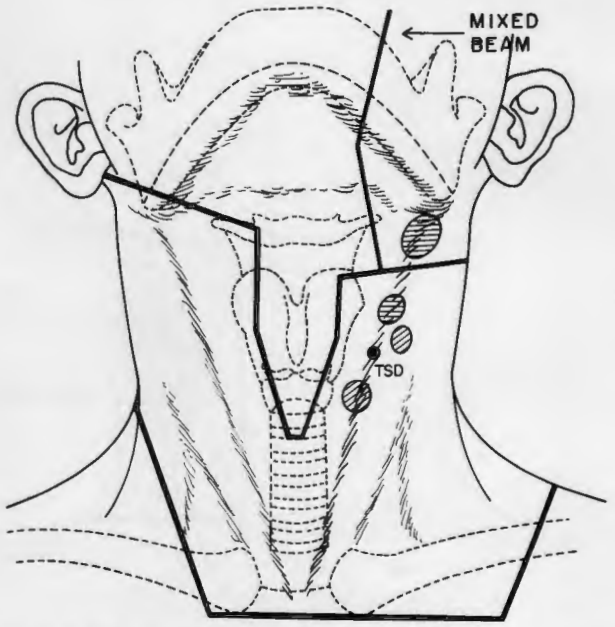

Figure 6-58. Portal arrangement to irradiate the opposite upper neck and both sides of the lower neck in conjunction with mixed photon and electron beam therapy to the primary lesion. TSD, target-to-skin distance.

there is a large upper neck node, and a decision must be made as to placement of the junction line that separates the upper and lower neck portals. For primary lesions of the oral cavity, oropharynx, and nasopharynx, it is our practice to place the junction line through the positive lymph node, if necessary, to put the junction near the thyroid notch. Because these patients frequently have a neck dissection, it is not critical that the junction be placed to include the entire lymph node within the primary portals. Although this is not a frequent clinical situation, no treatment failures have been identified related to placement of the junction through a large node.

A lower neck portal designed to irradiate the contralateral neck when a mixed-beam technique is used for the primary lesion is shown in Figure 6-58. The contribution of the mixed-beam dose to the contralateral upper neck must be factored into the plan.

The preferred technique for adding additional irradiation to a large neck mass is shown in Figure 6-59. The lateral skin should be shielded when possible to reduce the risk of wound dehiscence if neck dissection is planned. The dose is concentrated at the neurovascular bundle, which is the area where the dissection is most critical.

The dose guidelines for squamous cell carcinoma metastatic to regional lymph nodes are given in Table 6-45. Split-course techniques resulted in a poorer control rate (see Table 6-44). Doses of 6200 cGy and at least 180 cGy per fraction (preferably 200 cGy per fraction) produce a high rate of control for lymph nodes 1 to 3 cm in diameter (Table 6-46).

Bataini and coworkers[9,10] reported a high rate of neck node control using a concomitant boost technique that delivered 1200 to 1500 cGy per week to the involved lymph nodes.

Postoperative Irradiation

The neck portion of the postoperative portals for oral cavity and oropharynx lesions is similar to those designed for treatment by irradiation alone (see Figs. 6-49*A* and 6-50*A*). However, it is necessary to cover the dissected areas within reason, and the portals are frequently large. It is almost always possible to place the junction between the primary portals and the low neck near the thyroid notch.

An example of postoperative portals after laryngectomy is shown in Figure 6-60.[2] The primary fields are treated through lateral parallel opposed portals. After administration of 4500 to 5000 cGy, a field reduction is made such that the spinal cord is no longer in the treatment field; the dose to high-risk areas behind the plane of the spinal cord may be boosted with 6- to 10-MeV electrons. (See Chap. 12 for dose recommendations for postoperative radiation therapy and Chap. 14 for the technique for the posterior cervical lymph node boost.)

The low neck, which includes the stoma, is treated as shown in Figure 6-60*B*. A spinal cord block is not necessary when this method is used. The dose at D_{max} in most patients is 5000 cGy in 25 fractions. In patients at high

TABLE 6-46. Control of Clinically Positive Lymph Nodes by Irradiation Alone*

Node Size (cm)	Lymph Node Control
≤1.0	21/22
1.5–2.0	25/25
2.5–3.0	12/13
3.5–6.0	7/11

* Minimum dose 6200 cGy and at least 180 cGy per fraction.
(Mendenhall WM, Million RR, Bova FJ. Analysis of time-dose factors in clinically positive neck nodes treated with irradiation alone in squamous cell carcinoma of the head and neck. Int J Radiat Oncol Biol Phys 1984;10:643)

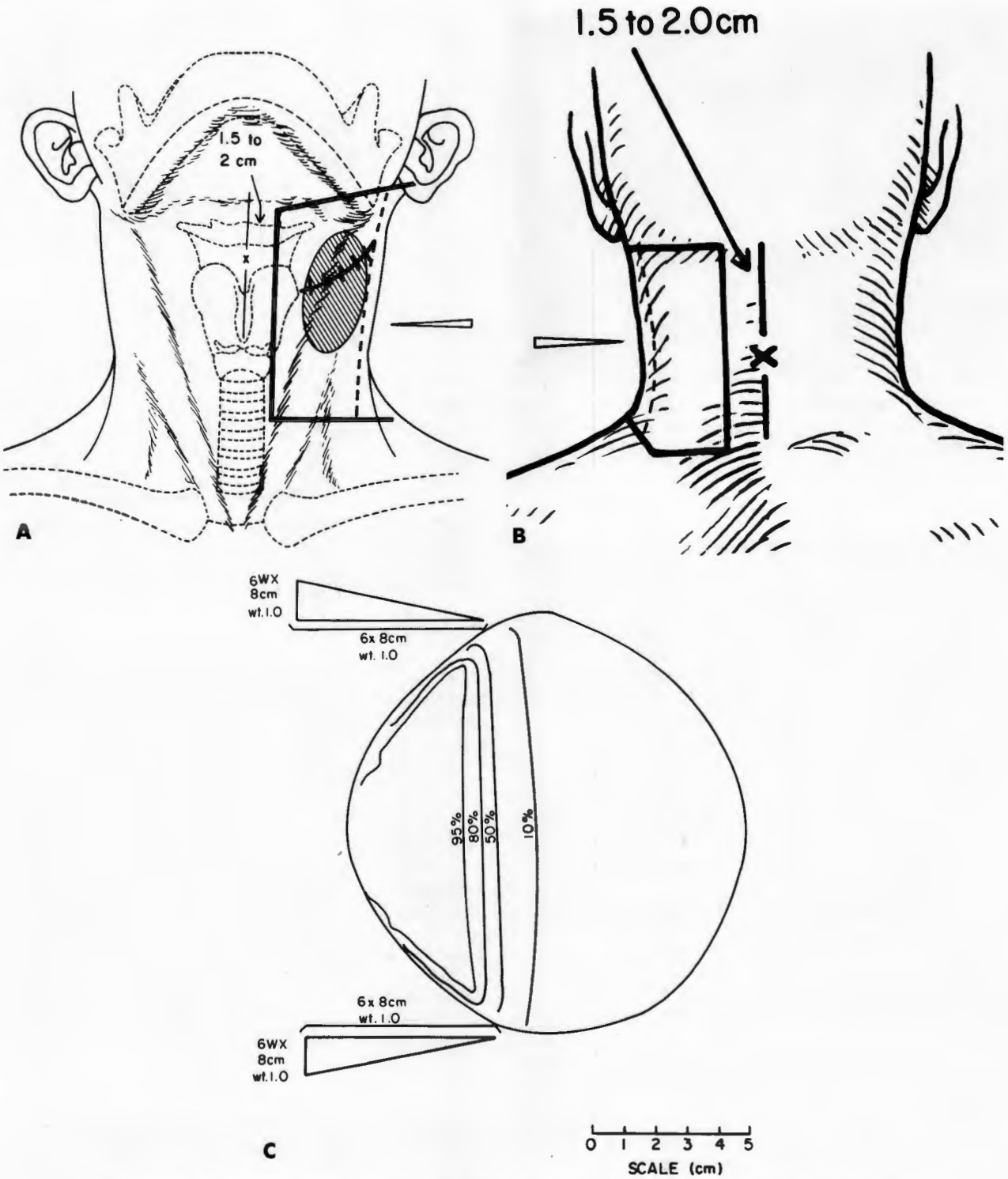

Figure 6-59. (*A* and *B*) Photon portals to boost dose to neck node. Parallel opposed anterior and posterior neck portals with wedges are used. The medial border is usually 1.5 to 2 cm from the midline. The dotted line represents the skin to be shielded unless there is skin invasion. (*C*) Isodose distribution, cobalt-60, 80 cm SSD.

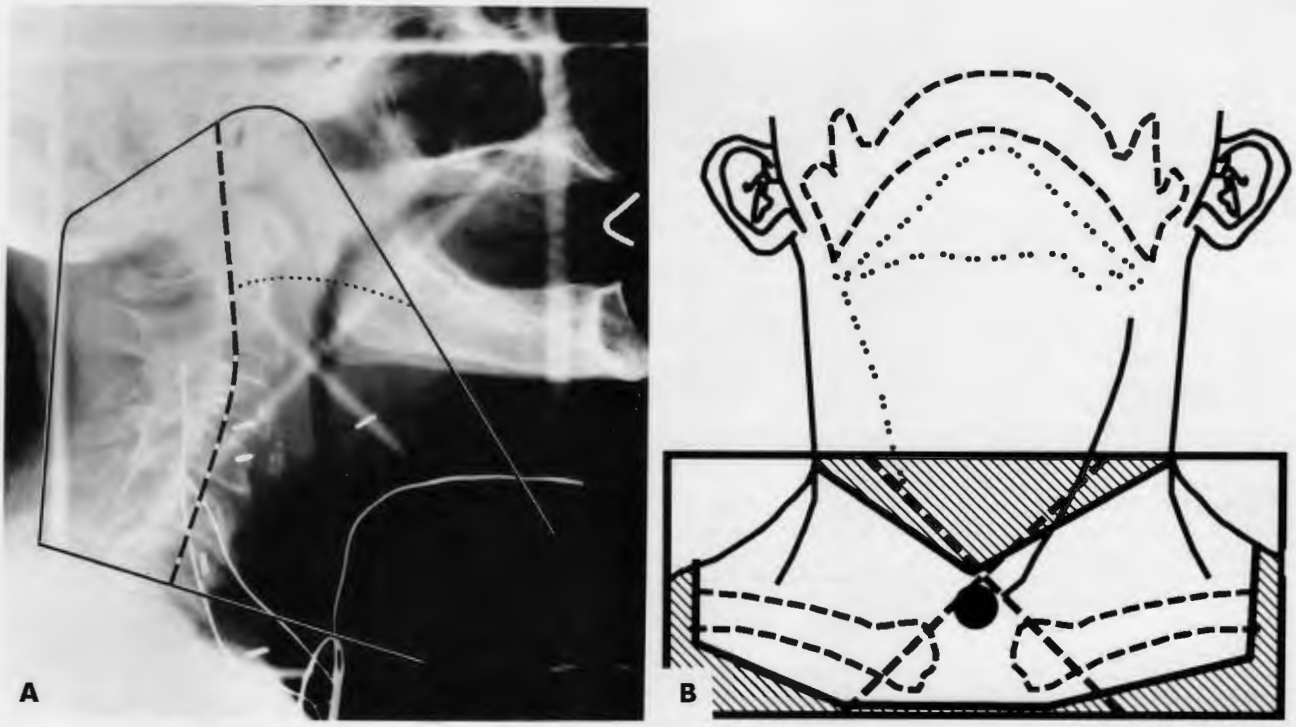

Figure 6-60. (*A*) Typical postoperative simulation film of a patient with advanced cancer of the laryngopharynx. The initial field reduction (after 5000 cGy, to shield the spinal cord) is indicated by the dashed line, and the final reduction (after 6000 cGy) is indicated by the dotted line. Wires mark the surgical scars and stoma. The slanting line used on the lower border reduces the length of spinal cord treated by the primary field, allows better caudal coverage of the mucosal surfaces while simultaneously bypassing the shoulders, and facilitates matching with the low neck field. (*B*) Schematic diagram of low neck field. The beam is vertical (0 degrees). The rectangle (*solid line*) represents the light field. The dashed lines denote the central axis. The shaded areas represent the blocked portions of the field (stacked lead blocks). The superior border of the neck field is the inferior border of the primary field. The actual line is treated only with the primary field. The upper border of the low neck field assumes a V shape. In the midline of the patient, the apex of the V generally is at or close to the central axis, so that the portion of the beam that irradiates the spinal cord is nondivergent. At the junction of the three fields, a short (2- to 3-cm) segment of the spinal cord remains untreated through any of the fields. (Amdur RJ, Parsons JT, Mendenhall WM, Million RR, Stringer SP, Cassisi NJ. Postoperative irradiation for squamous cell carcinoma of the head and neck: an analysis of treatment results and complications. Int J Radiol Oncol Biol Phys 1989;16:27)

risk for recurrence in the low neck (ie, who have positive low jugular nodes), a boost dose of 500 to 1000 cGy is given through a reduced field. In patients with subglottic extension, the dose to the stomal and peristomal tissues is boosted with electrons, usually 12 to 14 MeV.

The beams of choice are 4 MV and ^{60}Co, especially on the operated side, because of their buildup characteristics; higher energy beams may be undesirable because of underdosage of superficial tissues. A bolus (eg, petrolatum gauze) is placed on all scars and over drain sites. All scars, suture holes, and drain sites are treated with generous (2 to 3 cm) margins.

Techniques using anterior and posterior "minimantle" portals have the disadvantage of underdosage of lymph nodes near the base of the skull and either unnecessary irradiation of the posterior cranial fossa or a low dose in the base of the tongue. The thickest portions of the minimantle are at the extremes of the portal, and the dose distribution is unsatisfactory.

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GENERAL PRINCIPLES OF CHEMOTHERAPY

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Reports of the use of chemotherapy for patients with cancer of the head and neck appear to give a range of inconsistent, or even contradictory, results. The probability of tumor shrinkage, or *response*, is reported to be from about 10% to 80% when using similar drugs, and it may be difficult for the practicing oncologist to judge the merits of treatment from the confusing mass of data. Some of the differences in reported outcome are real: they depend on factors such as intensity of treatment and quality of care, and on the population of patients who are treated. It has been established that patients who are untreated have a much higher probability of response to chemotherapy than patients who relapse after primary treatment with surgery, radiation therapy, or both; also, performance status is an important determinant of response. Other differences in reported outcome are artifactual: they arise because of errors in tumor measurement, variability in criteria that are used to define tumor response, inappropriate exclusion of patients, and other factors related to the design and analysis of clinical trials. Also, although tumor response is an index of the biologic activity of drugs that is particularly important for the initial evaluation of new agents in phase II trials, it is not a direct indicator of benefit to patients. The more important endpoints of patient benefit are duration of survival and quality of survival.

To dissect the large amount of information relating to chemotherapy for cancer of the head and neck, the role and limitations of various types of clinical trials must be recognized. This chapter, therefore, initially reviews issues related to the design, analysis, and reporting of clinical trials; whereas subsequent sections review clinical trials that have given important information about the role of chemotherapy in palliation of advanced disease, and the potential for chemotherapy to contribute to a combined-modality approach in management of cancer primary to the head and neck.

PRINCIPLES OF CLINICAL TRIALS INVOLVING CHEMOTHERAPY

Endpoints of Clinical Trials

Survival

If chemotherapy conveys clinical benefit to patients it must be shown to increase either the duration or quality of survival. Duration of survival depends on stage and grade of disease, tumor bulk and sites of involvement, performance status, and other prognostic factors, in addition to the effects of treatment. A comparison of survival curves for patients treated in nonrandomized clinical trials, therefore, does not give useful information. The only exception is the demonstration of long-term survival for a subgroup of patients with metastatic cancer of the head and neck, but with the possible exception of nasopharyngeal cancer, this does not appear to be an achievable goal. Comparison of survival is particularly important when two or more groups of patients are compared in a randomized trial, and when chemotherapy is used as part of combined-modality treatment with curative intent, survival should be regarded as the primary endpoint.

Survival should be reported for all patients entered in a clinical trial, regardless of treatment received. Most clinical trials are best designed to evaluate the policy of giving a certain treatment, and exclusion of patients after entry introduces bias. Many authors have reported cause-specific survival and have excluded deaths that are apparently unrelated to cancer, such as accidents or myocardial infarction. Patients with cancer of the head and neck often have additional medical problems, social problems, or both, that place them at higher risk of death from other causes than an age-matched population, but absolute survival should always be reported as well as cause-specific survival. Otherwise, indirect adverse ef-

fects of chemotherapy (eg, heart failure associated with fluid loading) may be excluded.

Some investigators have claimed benefit for chemotherapy by demonstrating longer survival of responding patients (those with tumor shrinkage) than for nonresponding patients. This observation almost always can be made, both in treatment of recurrent or metastatic disease and when chemotherapy has been used before surgery, irradiation, or both for locally advanced disease. It does not, however, imply a cause and effect relation.[3] Survival may, indeed, be longer in responding patients because of the effects of chemotherapy; alternatively, patients who have a better prognosis may be more likely to respond to drug treatment, and would have had better survival even in the absence of such treatment. Resolution of these alternatives can only be achieved by comparing in a randomized trial the overall survival of groups of patients who do and do not receive chemotherapy.

Quality of Life

Even if chemotherapy does not lead to detectable increases in the duration of survival, it might relieve pain and other symptoms with consequent improvement in quality of life. This is a major goal when chemotherapy is used with the intent of palliating patients with metastatic cancer. Quality of life is multidimensional, and its assessment requires the use of validated questionnaires. Such questionnaires, or *instruments*, have been developed and used for other types of malignancy,[20,46,50] but have not been incorporated into clinical trials of chemotherapy for cancer of the head and neck. Since the major aim of treatment for recurrent or metastatic disease is palliation, validated endpoints to assess palliation must be used in future trials of chemotherapy for this group of patients.

Tumor Response

Shrinkage of tumor as a result of chemotherapy is an essential prerequisite for improvements in quality or duration of survival; in contrast, the observation of tumor response cannot be assumed to convey clinical benefit, especially when treatment is associated with toxicity. The demonstration that a drug, or drugs, cause a reasonable probability of tumor response in a phase II trial thus should be regarded only as generating a hypothesis that the treatment is clinically beneficial. This hypothesis must then be evaluated by comparing the new treatment with a standard approach in a randomized trial where the appropriate endpoints are survival and quality of life.

The assessment of tumor response is subject to considerable error. To determine the magnitude of measurement error, Warr and coworkers asked several physicians to measure perpendicular diameters of cervical lymph nodes in patients within a 36-hour interval, and compared these measurements.[73] Comparison of pairs of measurements of the cross section of identical lesions showed that on about 13% of occasions the second measurement of the pair was less than 50% of the first; if determination of partial response (PR) depends only on the demonstration of 50% shrinkage in cross section between an initial and one subsequent evaluation, then measurement error alone may lead to a false rate of PR of about 13%. Considerable variability also is found in the criteria that are used to assess tumor response.[67] Whereas most investigators require a 50% shrinkage in a cross-sectional area for PR, variability exists in definition of start and end of response, frequency of measurement, number of evaluations required to determine response, and criteria for multiple lesions and for lesions that cannot be measured. These factors, as well as variable exclusion of patients, were shown to lead to large differences in the reported rate of response when criteria used by different authors were applied to a single set of data.[5,67] Comparing rates of tumor response for different series of patients, therefore, cannot be used to assess the relative merits of different drug regimens.

In general, the rates of tumor response reported in clinical trials conducted by cooperative oncology groups tend to be lower than those reported from the use of identical chemotherapy in single institutions. Although this may be due, in part, to selection of patients and better patient care by a committed group in a single institution, it also reflects the quality control that has been developed by the cooperative groups. Such quality control includes well-defined and rigorous criteria of response, inclusion of all patients, and peer review of data. Experience of these groups is likely to reflect the expected rate of tumor regression when treatments developed in a single institution are exported to the community.

Nonrandomized Clinical Trials

Randomized trials are required to provide rigorous evaluation of the clinical value of new approaches to treatment, but their size and cost provides a severe limitation on the number of new treatments that can be evaluated in this way. Nonrandomized trials, therefore, have an important place in the development of new treatments, although only in settings where there are quantum leaps in the effectiveness of new treatment can they be used as definitive evidence of improved therapeutic benefit. This is not likely to occur from chemotherapy of cancer of the head and neck. Single-arm trials, therefore, should be used to assess feasibility and to generate hypotheses about benefits of new treatments.

New agents that have demonstrated ability to kill cancer cells in tissue culture and animal models receive their initial evaluation in phase I trials. The goal of such trials is to determine a maximal tolerated dose and to assess the toxicity and pharmacokinetics of treatment. Increasing doses are administered to small groups of volunteer patients with a variety of malignant diseases for whom no standard treatment is available, and dose escalation is stopped when a certain level of toxicity is found.

Phase II trials evaluate biologic activity of new drugs or drug combinations for patients with a given type of malignant disease. For new agents, patients with cancer of the head and neck are treated at the maximum tolerated dose determined from phase I trials and the primary endpoint is tumor response. Only patients with measurable lesions, who can be evaluated for tumor response, usually are included. Traditionally, new agents have been rejected for further study if the probability of response is less than 20%; if a phase II trial demonstrates no responses among 14 patients, usually it is terminated because one can be fairly certain that the true response rate in a larger trial would not exceed 20% ($P < .05$). If more responses are found the trial usually is enlarged, or

additional phase II studies are conducted, where the new agent is used in combination with other drugs. Again, the demonstration of tumor responsiveness is not equivalent to the demonstration of clinical benefit. As stated previously, a number of factors invalidate comparisons between rates of survival or tumor response between series of patients treated in different single-arm trials. The deliberate or inadvertent selection of patients with different prognostic factors, and variability in criteria of response and quality of care, are major reasons for not comparing rates. Two additional factors are publication bias and stage migration.

Publication bias refers to the greater probability that investigators will report, and journals will publish, clinical trials that show improvements in therapy compared with those that do not.[58] This leads to bias in the published literature in favor of positive trials.

Stage migration refers to the effect of newer and more sensitive diagnostic tests to detect small deposits of disease and to move patients into a higher stage.[9,27] This effect invalidates stage-by-stage comparison with historical controls. Because patients with relatively advanced disease, formerly assigned to a given stage, may now be upstaged, the effect of stage migration may be to show an apparent improvement in each *stage* of disease, without any change in outcome for the overall population. This paradox is illustrated in Figure 7-1.

Randomized Trials

Therapeutic approaches that appear to be highly promising in phase II trials should be selected for evaluation in randomized phase III trials to assess whether they convey greater therapeutic benefit than standard treatment. When new treatments are used to palliate patients with recurrent or metastatic disease, the standard treatment might be best supportive care, or treatment with methotrexate, which can be given with limited toxicity. When chemotherapy is used with irradiation, surgery, or both, then standard treatment should be the same local–regional therapy given alone. If chemotherapy is used concurrently with irradiation, however, it often leads to increased normal tissue reactions, and it may be more appropriate to compare the combined-modality approach with a somewhat higher dose of radiation used alone, so that survival can be compared at roughly equal levels of normal tissue toxicity.

The sample size required in a randomized clinical trial depends on the difference in outcome (eg, survival at a specified time) that is to be detected or ruled out with given levels of certainty, and on the expected outcome in the control group. The probability that a measured difference in survival could have occurred by chance alone is called the type I error; the probability of the trial detecting a real difference in outcome of a specified amount is known as its power $(1 - \beta)$, where β is referred to as the type II error. Standard tables can be used to estimate sample size (eg, see Gehan and Schneiderman[30]). Detecting or ruling out a 15% difference in absolute survival at a given time of follow-up, with usual values of $P = .05$ and $1 - \beta = .90$, typically requires about 250 patients. When the population is heterogeneous, which usually is the case for cancer of the head and neck, differences in outcome among subgroups in each arm often are larger than the overall improvement in survival that can be contemplated from use of chemotherapy. This heterogeneity can be allowed for, in part, by stratification of patients by known prognostic factors. Use of more than two or three strata is not useful, however, because subgroups then are too small, and a larger sample size than that estimated from standard tables may be required to allow for differences in distribution of other known or unrecognized prognostic factors. Also, it is usual and preferable to evaluate statistically the differences between survival curves rather than survival rates at one particular time.

Few randomized trials have been performed that are large enough to detect or rule out differences in survival that might be expected to occur from chemotherapy. Most trials have been reported as showing no significant difference in outcome, but are too small to rule out differences that would be regarded as clinically important. Smaller trials can be useful if survival rates of patients in

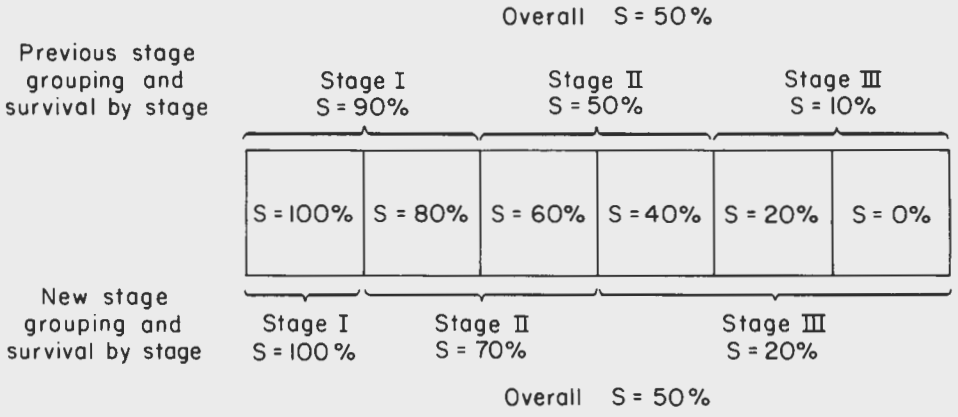
Overall S = 50%
Previous stage grouping and survival by stage
Stage I S = 90%
Stage II S = 50%
Stage III S = 10%
S = 100%
S = 80%
S = 60%
S = 40%
S = 20%
S = 0%
New stage grouping and survival by stage
Stage I S = 100%
Stage II S = 70%
Stage III S = 20%
Overall S = 50%

Figure 7-1. Stage migration. The figure indicates a hypothetical example in which patients are divided into six equal groups, within which the survival rate varies from 0% to 100%. The overall survival rate is 50%. Introduction of more sensitive staging investigations moves patients into higher stage groupings as shown, and there is an apparent improvement in survival for stages I, II, and III. The overall survival rate of 50% remains unchanged, however. (Tannock IF. Combined modality treatment with radiotherapy and chemotherapy. Radiother Oncol 1989;16:85)

the experimental arm show a nonsignificant trend to being *poorer* than for the control arm, and where confidence limits allow the exclusion of an improvement in survival of a specified amount from the experimental treatment. This has occurred in some trials where chemotherapy has been given to improve the results of irradiation, surgery, or both.[42,62,68] Relatively small trials that test similar strategies also can be combined in a metaanalysis. Differences in outcome that are not significant in individual trials may prove to be significant when the trials are combined. The method must be used cautiously, because publication bias may lead to a higher probability of inclusion of apparently positive trials, and because the overall results depend on methodologic rigor in individual trials. A metaanalysis of various types of chemotherapy used as an adjunct to irradiation, surgery, or both, for locally advanced disease, has been performed by Stell and Rawson, and is reviewed in a subsequent section.[61]

The preceding sections have indicated that meaningful improvements in therapeutic outcome must be demonstrated in large randomized clinical trials. The following review of results of chemotherapy for metastatic or recurrent disease, as part of the treatment for locally advanced disease, emphasizes this type of trial.

CHEMOTHERAPY FOR RECURRENT OR METASTATIC DISEASE

Squamous Cell Cancer

Clinical trials for squamous cell cancer usually have included a heterogeneous group of patients, and substantial differences may exist in the probability of tumor response among certain subgroups (see below). The results of some of the larger randomized trials are summarized in Table 7-1. Including patients with a variety of prognostic factors tends to lead to an "average" outcome, but even in these trials, differences in criteria for inclusion of patients will occur, and it is not valid to compare outcome measures between the different trials.

Methotrexate is the drug that has been used most extensively for treatment of cancer of the head and neck. In large cooperative group studies, treatment with intravenous doses of 40 to 60 mg/m^2/wk leads to response rates in the range of 10% to 35%, but median duration of response usually is short, about 2 to 5 months. Three studies have compared different doses of methotrexate used with or without leucovorin rescue,[17,72,77] but no trend to improvement in survival is shown when higher doses of methotrexate are used with leucovorin. Recent evidence suggests that leucovorin abrogates not only toxicity, but also antitumor effects of methotrexate.[8] A number of single agents have been reported to have activity in phase II clinical trials, but response rates generally have been equal to or lower than those reported for methotrexate, and often have been associated with more toxicity. Single agents with low but definite activity include cisplatin and bleomycin, but two randomized trials comparing methotrexate given intravenously or intramuscularly in conventional doses with intravenous cisplatin (50 mg/m^2 on days 1 and 8 of a 4-week cycle) found either lower or equivalent response rates for cisplatin, and remissions were short.[32,35] In two British trials, patients were randomized to cisplatin alone or with another drug, bleomycin alone (first trial only), methotrexate alone at a low dosage (second trial only), or a no-chemotherapy arm (first trial only).[10,51] Not all patients who were randomized to receive chemotherapy received their drugs, but the groups were compared on the basis of intended treatment. In both trials, survival rates were higher for patients assigned to receive cisplatin (alone or with other drugs), but both the number of treated patients in each arm and the reported differences in survival were small; also, the statistical analysis was suspect because of failure to correct for multiple comparisons between the groups.

Single-agent methotrexate has been compared with drug combinations in four large cooperative group trials (see Table 7-1). Cisplatin-based combination chemotherapy was shown to give a higher response rate in two large randomized trials: 48% for methotrexate, bleomycin, and cisplatin versus 35% for methotrexate alone in an Eastern Cooperative Oncology Group trial[71]; and 32% for cisplatin and 5-fluorouracil (5FU) by infusion versus 10% for methotrexate alone in a Southwest Oncology Group study.[28] Unfortunately, the increased rate of response with combination chemotherapy was not associated with improved survival rates in either trial, but combination chemotherapy was associated with greater toxicity. Neither trial included a formal assessment of quality of life, but it seems unlikely that available drug combinations convey increased therapeutic benefit compared with methotrexate alone. Moreover, the infrequent responses and their short duration in these trials suggest that these patients might have been managed as effectively with supportive care, although this has not been tested formally in a large study.

The clinical trials summarized in Table 7-1 have included a heterogeneous group of patients, and they might conceal the presence of small subgroups who derive greater benefit from treatment. The dominant factors that tend to increase the probability of response to chemotherapy are a high performance status of the patient,[2,31,71] lack of prior treatment with irradiation or surgery, absence of fixed nodes, and a nasopharyngeal primary tumor. One group of patients who should be offered chemotherapy routinely are those with metastatic or recurrent undifferentiated tumors of the nasopharynx. These patients have disease that may be associated with prior exposure to the Epstein-Barr virus, and usually are young or middle aged, without other underlying medical or social problems. The disease has a high incidence in people in or from China and southeast Asia, and from countries bordering on the Mediterranean sea. Chemotherapy incorporating cisplatin with other drugs, such as bleomycin, doxorubicin, or both, has a high probability of leading to response, and a small proportion of such patients have complete responses that are sustained for at least 3 years.[7,12] Further trials with longer follow-up are required to determine whether a small subset of these patients may be cured by chemotherapy.

With the exception of small subgroups of patients such as those with poorly differentiated tumors of the nasopharynx, the current data indicate a limited role for chemotherapy in palliation of recurrent or metastatic squamous cell cancer of the head and neck. Chemotherapy should not be regarded as part of standard management and most patients who wish to undergo a trial of drug treatment should be encouraged to take part in phase II trials that evaluate new agents.

TABLE 7-1. Larger Randomized Trials That Have Evaluated Chemotherapy for Patients With Recurrent or Metastatic Squamous Cell Cancer of the Head and Neck

References*	Drug Regimen†	Patients	Response Rate (%)	Median Duration (mo)	Survival
SECSG (Vogler et al,[72] 1979)	Methotrexate (weekly × 12)	154		Not stated	No difference
	500 mg/m² PO + leucovorin		22		
	60 mg/m² PO		27		
	60 mg/m² IV		31		
Woods et al,[77] (1981)	Methotrexate + leucovorin (weekly)	72			No difference; greater toxicity with highest dose
	5 g/m²		45	4	
	500 mg/m²		26	2	
	50 mg/m²		26	1.5	
ECOG (De Conti and Schoenfeld,[17] 1981)	Methotrexate (40–60 mg/m² weekly)	237	26	3	Favored low-dose methotrexate
	Methotrexate (240 mg/m² every 2 wk) and leucovorin		24	1.5	
	Methotrexate, cyclophosphamide, and Ara-C		18	1.5	
SWOG (Grose et al,[32] 1985)	Methotrexate (15 mg/m² IM for 3 d every 3 wk)	100	16	4.5	No difference
	Cisplatin (50 mg/m² on days 1 and 8 every 4 wk)		8	2	
NCOG (Jacobs et al,[37] 1983)	Cisplatin (80 mg/m² every 3 wk)	79	18	7	No difference
	Cisplatin + methotrexate (250 mg/m² weekly) + leucovorin		33	4	
SECSG (Williams et al,[75] 1986)	Methotrexate (45–60 mg/m² weekly)	190	16	5	No difference
	Cisplatin, vinblastine, bleomycin		24	4	
ECOG (Vogl et al,[71] 1985)	Methotrexate (40–60 mg/m² weekly)	163	35‡	4	No difference
	Methotrexate, cisplatin, bleomycin		48	5	
Morton et al,[51] (1985)	No chemotherapy	116	—	Not stated	Trend to improved survival in cisplatin arms
	Bleomycin (15 mg/d for 5 d, monthly)		14		
	Cisplatin (100 mg/m² monthly)		13		
	Bleomycin + cisplatin		24		
Campbell et al,[10] (1987)	Methotrexate (40 mg/m² every 2 wk)	124	19	Not stated	Favors cisplatin arms
	Cisplatin (100 mg/m² monthly)		40		
	Cisplatin + methotrexate		31		
	Cisplatin + 5FU (1 g/m² for 4 d monthly)		33		
EORTC (Clavel et al,[15] 1987)	Methotrexate, bleomycin, vincristine	185	28	4	No difference
	Same + cisplatin		50‡	7	
Jacobs et al,[36] (1992)	Cisplatin (100 mg/m² every 3 wk)	249	17	Not stated	No difference
	5FU (1 g/m² for 4 d every 3 wk)		13		
	Cisplatin + 5FU		32‡		
SWOG (Forastiere et al,[28] 1992)	Methotrexate (40–50 mg/m² weekly)	277	11	4	No difference
	Cisplatin (100 mg/m²) + 5FU (1 g/m² for 4 d), every 3 wk		30‡	5	
	Carboplatin (300–360 mg/m²) + 5FU, every 4 wk		18	5	

Ara-C, cytarabine; PO, by mouth; IV, intravenously; IM, intramuscularly; 5FU, 5-fluorouracil.

* Cooperative groups are ECOG, Eastern Cooperative Oncology Group; EORTC, European Organization for Research and Treatment of Cancer; NCOG, Northern California Oncology Group; SECSG, Southeastern Cancer Study Group; SWOG, Southwestern Oncology Group.

† Drugs were given intravenously unless otherwise stated.

‡ Differences in response rate between two of the arms were significant at $P < .05$ in these four studies. There were no significant differences in response rate in other trials.

Tumors of the Salivary Glands

Most tumors originating in the head and neck are squamous cell carcinomas, but a lower incidence of tumors with a variety of different histologic types exists, including lymphomas, sarcomas, and tumors originating in major or minor salivary glands. Although uncommon, these tumors occur in young or middle-aged people, and have a higher probability of metastasis to the lungs and elsewhere than squamous cell carcinomas.

Experience with chemotherapy is limited for metastatic tumors of the salivary glands. In a review of the

literature and a survey of various institutions, Suen and Johns collected data on 85 patients who had been treated with chemotherapy, and reported an overall response rate of 42% with 10% clinical complete remissions.[63] This rate of response is subject to the problems associated with a retrospective review, and may be regarded as an upper limit of what might be reported if a similar group of patients were treated in a rigorously conducted prospective trial; it indicates, however, that some patients have tumors that are responsive to chemotherapy. The majority of patients in this review had adenoid cystic carcinoma (53 of 85) with small numbers in each of the other subtypes; responses were observed among patients with each histologic subtype, but numbers are too small to indicate trends in responsiveness. Small individual series have reported a consistent rate of response (36% to 46%) to cisplatin-based chemotherapy.[16,21,69]

Many patients with salivary gland tumors develop slowly growing pulmonary metastases that may remain asymptomatic for months, or even years. These patients should be observed. For symptomatic patients it is reasonable to offer a trial of palliative chemotherapy using a cisplatin-containing drug regimen.

CHEMOTHERAPY USED AS AN ADJUNCT TO SURGERY AND RADIATION THERAPY

Clinical trials have investigated the use of chemotherapy before surgery or radiation therapy (known as induction or neoadjuvant chemotherapy), concurrent with radiation therapy, or for patients at high risk of recurrence who have no evidence of disease after local treatment with radiation therapy or surgery (adjuvant chemotherapy), as shown in Figure 7-2. The major aim of the various types of adjunctive chemotherapy is to improve survival rates, but mechanisms are likely to be different from those that have allowed improved survival rates in premenopausal women with breast cancer, or in young patients with osteogenic sarcoma. In those diseases, a high rate of failure in distant metastatic sites occurs, and adjuvant chemotherapy exerts its therapeutic effect through eradication of occult metastases. Distant metastases occur rarely in cancer of the head and neck in the absence of local or nodal recurrence[48] (Table 7-2). Even if chemotherapy reduced the rate of metastatic failure to zero, it would take large trials to detect an improvement in overall survival, with the possible exception of trials for nasopharynx tumors, where metastatic failure is more common. If adjunctive chemotherapy is to improve survival rates of patients with cancer of the head and neck, it must complement the effects of surgery and irradiation to increase the probability of disease control in the primary site and in the neck.

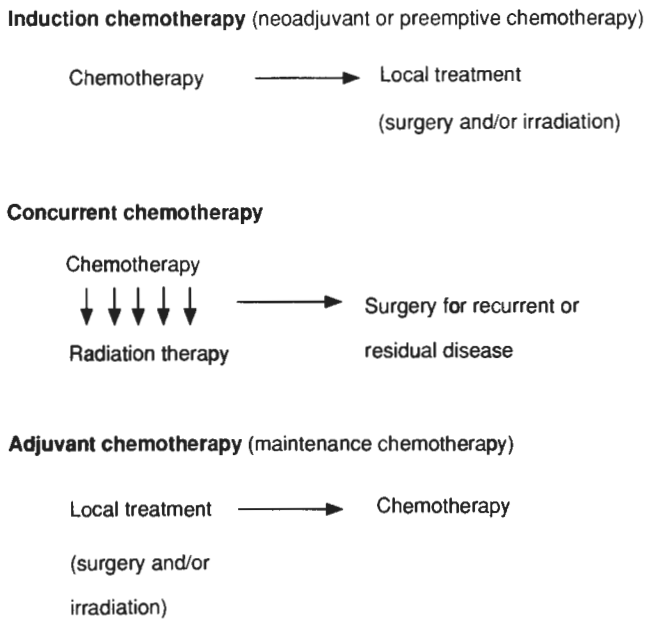

Figure 7-2. Various types of adjunctive chemotherapy that have been used in the treatment of locally advanced head and neck cancer. Combinations of these approaches have been tested in some clinical trials.

TABLE 7-2. Percentage of Patients with Head and Neck Cancer Who Relapse Only in Distant Sites

	Patients	Distant Relapse Only (%)
Oral cavity	1710	1.8
Oropharynx	1098	6.6
Nasopharynx	224	17.4
Paranasal sinus or nasal cavity	230	3.0
Supraglottic larynx	466	9.2
Vocal cord	858	0.8
Hypopharnyx	433	14.5
All T1–2	2516	3.6
T3–4	2503	6.8
All N0	3004	1.6
N+	2015	10.6

(Adapted from Merino OR, Lindberg RD, Fletcher GH. An analysis of distant metastases from squamous cell carcinoma of the upper respiratory and digestive tracts. Cancer 1977;40:150)

The following sections review the results of randomized clinical trials that have evaluated the role of chemotherapy in each of the sequences shown in Figure 7-2, together with aspects of tumor biology that relate to the use of such treatment.

Induction Chemotherapy

When patients with locally advanced cancer of the head and neck receive initial treatment with chemotherapy, the probability of tumor response is higher than for patients who have recurrent or metastatic disease after completion of local therapy. Reports from single institutions have indicated response rates of 70% to 90%, with complete clinical responses of 20% to 50% when patients have been treated with aggressive cisplatin-based regimens.[22,23] Up to 40% of patients who achieve clinical complete response have no detectable tumor in surgical specimens after resection of the previously involved area.[1] Patients who have a good response to chemotherapy almost invariably have a better prognosis than those who do not respond. These results do not prove the value of chemotherapy, but they encourage the belief that chemotherapy increases the probability of cure. They have

unfortunately led to the widespread use of induction chemotherapy outside the setting of clinical trials, which offer the only method for evaluating the long-term effects of such treatment.

Results of randomized, controlled clinical trials that have evaluated the results of induction chemotherapy are summarized in Table 7-3. The initial rate of complete response to chemotherapy evidently is lower than that reported from single institutions, even in recent trials where aggressive chemotherapy has been used. This may reflect selection of patients, the higher intensity of treatment, or both, that may result from the care of a committed team. Many of the trials have methodologic limitations, such as exclusion of patients after randomization; some have been reported only in abstract form; and some have follow-up that is too short to be definitive. Most are too small to detect clinically relevant differences in survival.[14] Despite these limitations, the results are disappointing: no overall trend is shown for improvement in survival rates among patients who were randomized to receive induction chemotherapy.

Many of the trials that are summarized in Table 7-3 used chemotherapy that is now considered to be suboptimal. More recent trials have evaluated the use of aggressive regimens such as 5FU and cisplatin by infusion, or other cisplatin-based regimens that were associated with considerable toxicity. One of these trials was discontinued after entry of only 60 patients, because of a trend to poorer survival in patients receiving chemotherapy; in this trial, and in two others with similar trends, the authors were able to exclude a beneficial effect of chemotherapy on survival, and raised concerns about delay in initiation of effective local treatment.[62,68] Other trials that have evaluated the role of several courses of cisplatin-based chemotherapy have not indicated any consistent trends toward improvement in the probability of tumor clearance or survival in patients randomized to receive induction chemotherapy.

The metaanalysis of trials of induction chemotherapy undertaken by Stell and Rawson[61] involved pooling of results from publications describing many of the trials that are summarized in Table 7-3. The overall ratio of

TABLE 7-3. Larger Randomized Controlled Trials That Have Evaluated the Role of Induction Chemotherapy in Treatment of Patients With Locally Advanced Cancer of the Head and Neck

Authors	Patients	Follow-Up (Years)	Type of Chemotherapy	Response to Chemotherapy		Influence on Survival
				Total (CR + PR)	Complete (CR)	
Knowlton et ol,[41] (1975)	96	5	Methotrexate	NS	NS	No difference
Fazekas et al,[26] (1980)	638	5	Methotrexate	NS	NS	No difference (favors chemotherapy)
Stell et al,[62] (1983)	86	2.5	Seven drugs (2 cycles)	NS	NS	No difference (favors control arm)
Arcangeli et al,[4] (1983)	142	5	Intraarterial methotrexate	NS	NS	Improved survival with chemotherapy ($P < .05$)
Taylor et al,[66] (1985)*	82	3	Methotrexate + leucovorin (1 cycle)	40	6	No difference
Kun et al,[42] (1986)	83	3	Bleomycin methotrexate, 5FU (2 cycles)	68	5	No differences (favors control arm)
Head and Neck Contracts Program[34] (1987)*	462	5	Cisplatin bleomycin, (1 cycle)	37	3	No difference
SWOG (Schuller et al,[56] 1988)	158	5	Cisplatin, methotrexate, bleomycin, vincristine (3 cycles)	70	19	No difference (favors control arm)
Carugati et al,[11] (1988)†	120	5	Cisplatin, bleomycin + methotrexate	52	NS	No difference (favors chemotherapy)
Martin et al,[47] (1988)†	107	2	Cisplatin, 5FU, bleomycin, methotrexate	49	6	Too early (disease-free survival favors control arm)
Paccagnella et al,[53] (1990)†	221	1–3	Cisplatin/5FU (4 cycles)	70	16	Too early (no difference in tumor clearance)
Jaulerry et al,[38] (1992)	100	5	Cisplatin, 5FU, vindesine, mitomycin C (2 cycles)	50	10	No difference
Jaulerry et al,[38] (1992)	108	2.5	Cisplatin, 5FU, vindesine (3 cycles)	70	22	No difference

NS, not stated; CR, complete response; PR, partial response; SWOG, Southwest Oncology Group; 5FU, 5-fluorouracil.

* All or some of the patients randomized to receive chemotherapy were also scheduled to receive adjuvant chemotherapy after local treatment.

† Reported only in abstract form.

rates of survival for patients randomized to receive induction chemotherapy compared with controls was 0.92 ± 0.11, a nonsignificant trend toward harmful effects of chemotherapy. This analysis also suggested no trend for patients to fare better after aggressive multiagent chemotherapy, although as stressed earlier, metaanalysis may be confounded by methodologic problems leading to bias in individual trials. Bias tends to operate in favor of experimental treatment, however. Neither individual trials nor the metaanalysis suggests therapeutic benefit from induction chemotherapy.

A randomized trial that does not involve a simple comparison of induction chemotherapy versus a control group was undertaken by the Department of Veterans Affairs Laryngeal Cancer Study Group (VA) in patients with advanced larynx cancer.[18] The design of this trial is illustrated in Figure 7-3. The results demonstrated equivalent survival in the two arms, with 64% of patients in the chemotherapy arm alive and well with an intact larynx. This trial has been interpreted as providing evidence for the value of chemotherapy in allowing laryngeal preservation. This conclusion cannot be justified, however, because randomized controlled studies have shown equivalence of disease control and survival rates for patients treated with radiation therapy alone, or induction chemotherapy followed by radiation therapy (see Table 7-3). Thus, patients treated in the chemotherapy arm of the VA study might have fared as well with a policy of using only primary irradiation with surgery reserved for salvage of residual or recurrent disease (as is performed in many Canadian and European centers). An important new study has been planned in which patients with advanced laryngeal cancer will be randomly assigned to recieve chemotherapy followed by radiation therapy (as in the VA trial), radiation therapy alone, or radiation therapy with concurrent cisplatin therapy, with strict guidelines for surgery if there is no response or if the disease persists.

Biologic Basis for Limitations of Induction Chemotherapy

The ability of induction chemotherapy to induce shrinkage of a tumor in a high proportion of patients with cancer of the head and neck, with no evidence for improvement in survival, is a disappointing enigma. Possible reasons for these discordant results on tumor response and survival follow.

Inadequate Cell Kill

A large tumor of the head and neck may weigh 10 to 100 g and contain 10^{10} to 10^{11} tumor cells. Reduction in cell number by chemotherapy to $\sim 10^9$ cells ($\sim$1 g of tumor) would be regarded as a good PR, and a residual cell number of 10^8 cells ($\sim$0.1 g) probably would escape clinical or radiologic detection and be assessed as a complete response. Because given doses of drugs and radiation tend to kill a given fraction of tumor cells, rather than a given number, leading to exponential cell survival curves, this visually impressive tumor response is a small step toward cure[64,65] (Fig. 7-4). Even a pathologically confirmed complete response may be consistent with the presence of $\sim 10^6$ viable tumor cells per gram of tissue, since it is unlikely that a pathologist can detect tumor cells that are dispersed among normal cells at a frequency of 1 in 1000 or less. Attaining tumor response after induction chemotherapy, therefore, may be consistent with a limited cell kill, a premise that is supported further by the short median duration of response that is observed after treatment of patients who do not go on to receive irradiation or surgery.

If the effects of chemotherapy are additive with those of irradiation and surgery, it remains to be explained, however, why drug effects do not at least contribute to improved survival rates.

Reduction in Surgical or Radiation Fields After Chemotherapy

Limited cell kill after tumor response to chemotherapy suggests that any anatomic region that is grossly involved with tumor at initiation of chemotherapy is likely to contain residual viable tumor cells, even if these are not evident by physical, radiologic, or even pathologic examination. Chemotherapy does not render an unresectable tumor operable for cure, therefore, and irradiation or surgical fields should encompass all areas of disease that were present before chemotherapy. Most clinical trials have stipulated this requirement, but particularly in multiinstitution trials, it may be difficult to

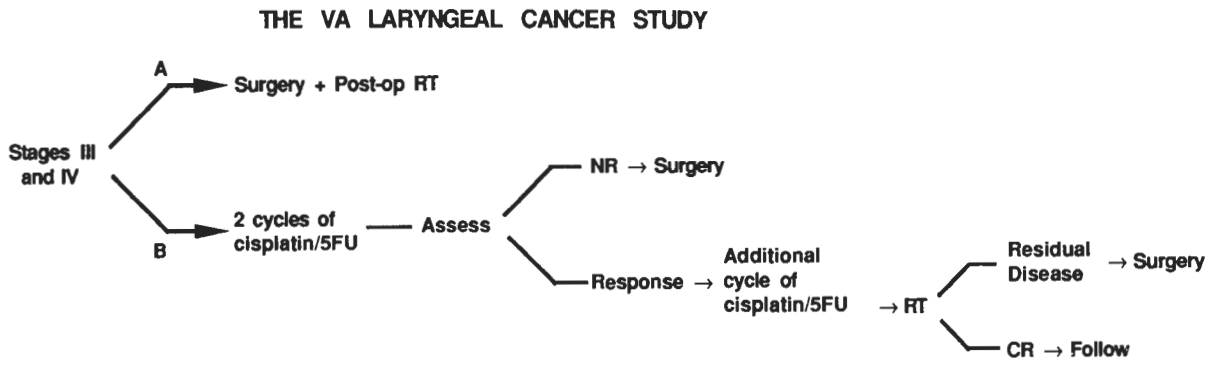

Figure 7-3. Design of the Veterans Administration Laryngeal Cancer Study Group Trial. Early results of the study show equivalent survival rates in the two arms, with about 60% of patients in arm B surviving with larynx intact. Failure of induction chemotherapy to improve survival in other studies (see Table 7-3), however, suggests that similar results might have been obtained in arm B by using initial radiation therapy alone.

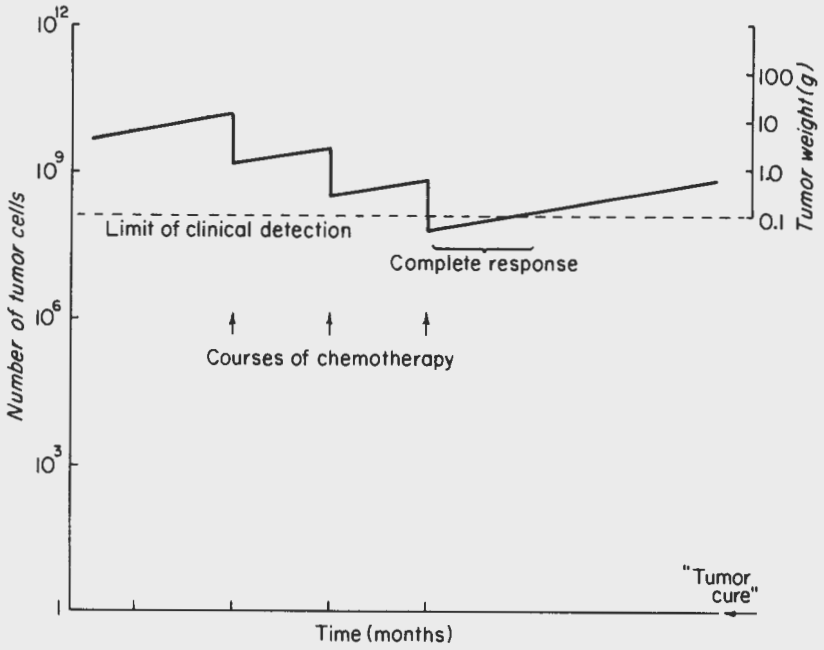

Figure 7-4. A hypothetical tumor containing 10^{10} viable cells (about 10 g) is treated with three courses of chemotherapy, each of which kills 90% of the cells. There is some repopulation between treatments. After three courses, the number of viable tumor cells is less than 10^{8} (about 0.1 g), and the patient is judged to be in complete clinical and radiologic remission. This is a small step toward tumor cure. Also, additional chemotherapy may not be helpful if drug-resistant cells have been selected after three courses of chemotherapy. (Tannock IF. Combined modality treatment with radiotherapy and chemotherapy. Radiother Oncol 1989;16:94)

ensure rigid adherence to this criterion. It is unlikely that reduction in the extent of local–regional therapy has been a major contributing factor in the disappointing results that have been observed after induction chemotherapy.

Reduction in Response to Radiation After Chemotherapy

Large tumors tend to be poorly vascularized, leading to regions of necrosis, as well as nutrient-deprived regions where the rate of cell proliferation is low. Shrinkage of tumor after chemotherapy might lead to improved vascularity. This can have opposing effects on subsequent response to irradiation: improvement in oxygenation would tend to increase responsiveness to irradiation, whereas an effect to induce more rapid proliferation of surviving tumor cells would be detrimental, as illustrated schematically in Figure 7-5.[64] Although no direct evidence exists for an effect of chemotherapy-induced shrinkage to stimulate proliferation in human tumors, this effect has been found to occur in tumors of rats and mice. It also is supported by the finding that when irradiation is used alone as the primary treatment for cancer of the head and neck, radiation dose must be increased if the duration of fractionation is prolonged beyond about 4 weeks, presumably because of increased proliferation of tumor cells after this time.[76] This observation suggests that the detrimental effects on radiation response from stimulation of tumor cell proliferation may outweigh any beneficial effects due to reduction in hypoxic function. Prior exposure to chemotherapy has been reported by some investigators to cause a decrease in the intrinsic radiosensitivity of cells.[45] This effect has been described after treatment with alkylating agents, cisplatin, and doxorubicin, but the effects are inconsistent and vary with the cell lines that have been studied. One possible mechanism may be drug-induced stimulation of glutathione synthesis, or induction of the enzymes glutathione-S-transferase and glutathione reductase, which are involved in the inactivation of radical species that are produced by some anti-cancer drugs as well as by ionizing radiation.[13] Direct investigation of the radiosensitivity of cells in tumors of the head and neck after initial chemotherapy would provide useful information about common mechanisms of therapeutic resistance.

Concurrent Treatment With Radiotherapy and Chemotherapy

Randomized controlled trials that have evaluated the role of concurrent radiotherapy and chemotherapy (with or without surgery) are summarized in Table 7-4. An additional trial from China showed improved disease-free survival for patients randomized to receive a Chinese herb concurrent with irradiation for nasopharyngeal cancer, compared with irradiation alone.[78] Most of the trials summarized in Table 7-4 do not show significant differences in survival, but several of them show trends to improvement in local control, survival, or both. These trends have been observed for concurrent treatment with bleomycin, cisplatin, 5FU, and mitomycin C, and most often have been observed for tumors of the oral cavity and oropharynx. An Italian trial has also shown a small but significant improvement in survival from the use of alternating courses of chemotherapy (cisplatin and 5FU) and radiation therapy, as compared with conventional radiation therapy alone.[49] Most of the trials have reported an increase in acute toxicity from use of chemotherapy, and there has been no evidence of reduction in metastatic failure.

Although the results summarized in Table 7-4 are encouraging, they do not provide definitive evidence for therapeutic benefit from chemotherapy. All but one of the trials compared treatment with the same irradiation dose and schedule as for radiation therapy used alone. An effect to increase local control at the expense of greater normal tissue reactions might have been achieved by using a higher dose of radiation without

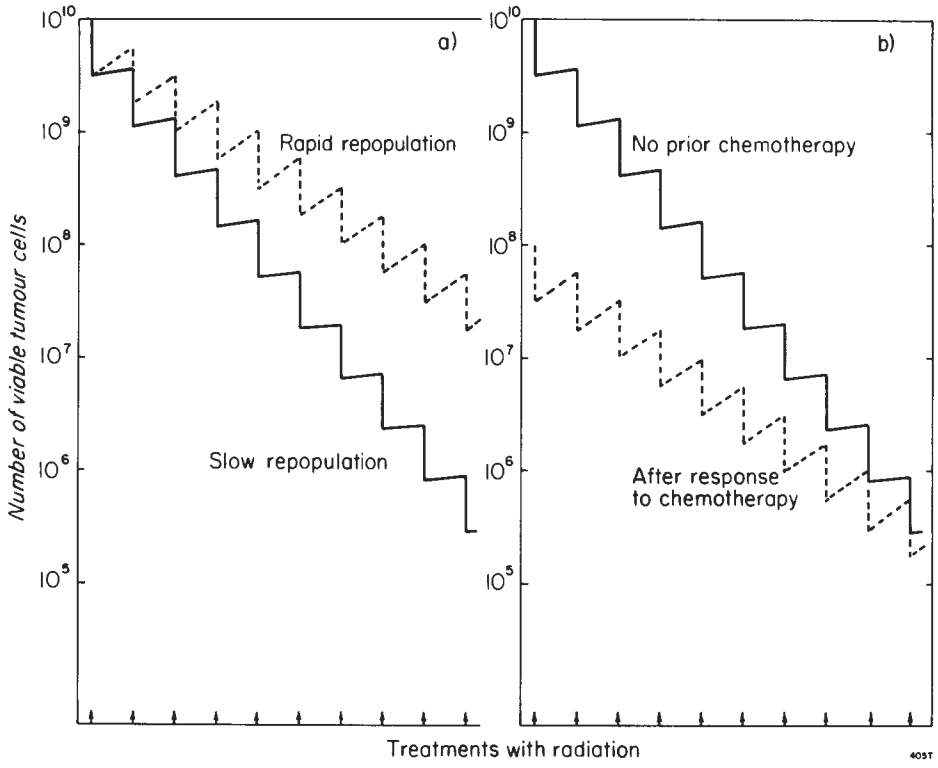

Figure 7-5. (*A*) Schematic illustration of the effect of cell proliferation between dose fractions on cell survival after fractionated radiation. The two curves are drawn with the same cell kill from each dose fraction but with differing rates of repopulation between dose fractions. (*B*) Solid curve indicates the expected survival of tumor cells during fractionated radiation therapy given to a previously untreated tumor. Dashed curve reflects the expected survival of tumor cells for radiation therapy given after induction chemotherapy if drug treatment leads to stimulation of cell proliferation after initial tumor response. There is no gain from combined treatment at the end of the course of radiation. (Tannock IF. Combined modality treatment with radiotherapy and chemotherapy. Radiother Oncol 1989;16:96)

TABLE 7-4. Larger Randomized Controlled Trials That Have Compared Radiation and Concurrent Chemotherapy With Radiation Alone for Primary Head and Neck Cancer

Authors	Patients	Follow-Up (Years)	Type of Chemotherapy	Influence of Chemotherapy
Stefani et al,[59,60] (1971, 1980)	150	10	Hydroxyurea	Poorer survival with chemotherapy ($P < .05$)
Lo et al,[44] (1976)	151	2–13	5FU	Local control and survival improved for oral cavity ($P < .05$); increased mucosal reactions
Shanta and Krishnamurthi[57] (1980)	157	5	Bleomycin	Oral cavity only; marked improvement in local control and survival ($P < .001$); increased mucosal reactions
Vermund et al,[70] (1985)	222	3–6	Bleomycin	No difference in local control or survival; increased morbidity
Fu et al,[29] (1987)	104	5	Bleomycin	Improved local control and trend to improved survival; increased morbidity
EORTC (Eschwege et al,[25] 1988)	199	10	Bleomycin	No difference in local control or survival; increased morbidity
Gupta et al,[33] (1987)	318	3	Methotrexate	Improved disease-free survival; improved survival for oropharynx cancer
Weissburg et al,[74] (1989)	120	5	Mitomycin C	Trend to improved disease-free survival; no difference in survival; increased morbidity
Keane et al,[39] (1988)*	212	1.5–6	Mitomycin C + 5FU†	No significant difference in any endpoint
Bachaud et al,[6] (1991)	83	2	Cisplatin	Improved local control and disease-free survival
Merlano et al,[49] (1992)	157	3	Cisplatin + 5FU	Improved survival ($p < 0.05$) with chemotherapy

5FU, fluorouracil; EORTC, European Orgonizotion for Research and Treatment of Cancer.
* Published in abstract form only.
† Split-course irradiation in chemotherapy arm only.

chemotherapy. In the trial where conventional radiation therapy was compared with a split course of treatment (leading to a lower effective dose) used with mitomycin C and 5FU, both survival and acute normal-tissue reactions were equivalent.[39] Few of the trials have analyzed late reactions in normal tissues that limit radiation dose. If chemotherapy has minimal effects to increase such reactions, it may, indeed, convey therapeutic benefit. Further trials should be performed where radiation dose is adjusted in the control arm to allow comparison of survival at equivalent levels of dose-limiting normal tissue toxicity.

Any beneficial effects of concurrent chemotherapy and radiation therapy may be due to added toxic effects of the two modalities, with less than additive effects against dose-limiting normal tissues. One mechanism might involve inhibition by drugs of cell proliferation, which may be stimulated in the tumor as shrinkage is accompanied by improved vascularity. This effect would lower the effective number of target cells to be killed by radiation therapy (compare with Fig. 7-5); similar effects may occur, however, in the surrounding mucosa.

It has been proposed that mitomycin C, which requires bioreduction for activity, may be beneficial because of selective effects against hypoxic tumor cells that are resistant to radiation.[74] Whereas selective toxicity of mitomycin C has been demonstrated against hypoxic cells in culture,[40] other effects such as limited penetration of the drug from tumor blood vessels have prevented the demonstration of selective killing of hypoxic cells in solid tumors of rodents.[54]

Chemotherapy Given After Radiation or Surgery

Only two large randomized controlled trials have evaluated the effects of chemotherapy administered after completion of local–regional treatment for cancer of the head and neck, and one trial has investigated the effect of the immune modulator levamisole (Table 7-5). Two of these trials show no difference in survival rates, and the other reports better survival in the control arm.[19,55] A major conclusion of these and other smaller trials is that it is difficult to administer chemotherapy to a substantial proportion of patients after radiotherapy, surgery, or both. Reasons for noncompliance include greater toxicity of the drugs when given after local treatment, especially in causing mucositis after radiotherapy, and lack of motivation in patients who have no clinically evident disease.

A large intergroup study was reported in which patients were randomly assigned to receive three courses of cisplatin and 5FU chemotherapy after complete resection of disease and before radiation therapy, or standard surgery and postoperative radiation therapy.[43] There was no difference in survival, but patients who received chemotherapy had a lower incidence of distant metastasis.

A few trials of induction or concurrent chemotherapy have included a policy of also giving adjuvant chemotherapy. The Head and Neck Contracts Program was designed as a three-arm trial in which patients received local–regional treatment only, induction chemotherapy (one course of bleomycin and cisplatin), and induction plus maintenance chemotherapy with cisplatin for 6 months.[34] There were no differences in survival, and there was poor compliance with maintenance chemotherapy: 9% of patients completed six cycles, and 27% completed three or more cycles. There was, however, a decrease in the incidence of distant failure for patients assigned to maintenance chemotherapy after local treatment. In another study, all patients received induction chemotherapy with cisplatin, bleomycin, and methotrexate, and those who had responded to chemotherapy and had no evident disease after local treatment were randomized to receive adjuvant chemotherapy or to be observed.[24] Although 144 patients were entered into the trial, a subset of only 46 patients could be randomized. The group receiving adjuvant chemotherapy had better survival rates. In view of the disappointing results of induction chemotherapy in randomized trials (see Table 7-3), it is difficult to justify the policy of using such treatment, even if it is confirmed in larger trials that a subset

TABLE 7-5. Three Randomized Controlled Trials That Have Evaluated the Results of Adjuvant Systemic Therapy Given After Locoregional Treatment for Cancer of the Head and Neck

Trial	No. of Patients	Follow-Up (Yr)	Type of Systemic Therapy	Result
Olivari et al,[52] (1979)	134	3	Levamisole	No difference in survival; increased recurrence in stage I and III patients receiving levamisole
Rossi et al,[55] (1988)	229	4	Vincristine, cyclophosphamide, doxorubicin for 6 mo	Nasopharynx cancer only; no difference in survival
Domenge et al,[19] (1988)*	287	3	Cisplatin (for 3 cycles), methotrexote, bleomycin (for 8 cycles)	Better survival in control arm ($P < .03$)

* Published only in abstract form.

of responding patients derive benefit from continuation of chemotherapy after irradiation, surgery, or both.

SUMMARY

The results of chemotherapy for all stages of cancer of the head and neck remain disappointing, and this modality should not be regarded as part of standard management. Selected patients with recurrent or metastatic disease (especially those with anaplastic tumors of the nasopharynx) may deserve a trial of cisplatin-based chemotherapy, but most patients either should be managed with supportive care, or encouraged to take part in phase II trials which evaluate new agents. No established role exists for chemotherapy as an adjunct to surgery, irradiation, or both for treatment of locally advanced disease, and it should not be used outside the setting of a clinical trial. Trials of induction chemotherapy have shown no trends to improve survival, and the most promising results have occurred in trials where radiation and drugs are administered concurrently. Randomized controlled trials should continue to evaluate chemotherapy used in this way, whereas other studies should seek to elucidate biologic mechanisms that influence the combined effects of drug treatment and local treatment with radiation or surgery.

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7

GENERAL PRINCIPLES OF CHEMOTHERAPY

IAN F. TANNOCK

Reports of the use of chemotherapy for patients with cancer of the head and neck appear to give a range of inconsistent, or even contradictory, results. The probability of tumor shrinkage, or *response*, is reported to be from about 10% to 80% when using similar drugs, and it may be difficult for the practicing oncologist to judge the merits of treatment from the confusing mass of data. Some of the differences in reported outcome are real: they depend on factors such as intensity of treatment and quality of care, and on the population of patients who are treated. It has been established that patients who are untreated have a much higher probability of response to chemotherapy than patients who relapse after primary treatment with surgery, radiation therapy, or both; also, performance status is an important determinant of response. Other differences in reported outcome are artifactual: they arise because of errors in tumor measurement, variability in criteria that are used to define tumor response, inappropriate exclusion of patients, and other factors related to the design and analysis of clinical trials. Also, although tumor response is an index of the biologic activity of drugs that is particularly important for the initial evaluation of new agents in phase II trials, it is not a direct indicator of benefit to patients. The more important endpoints of patient benefit are duration of survival and quality of survival.

To dissect the large amount of information relating to chemotherapy for cancer of the head and neck, the role and limitations of various types of clinical trials must be recognized. This chapter, therefore, initially reviews issues related to the design, analysis, and reporting of clinical trials; whereas subsequent sections review clinical trials that have given important information about the role of chemotherapy in palliation of advanced disease, and the potential for chemotherapy to contribute to a combined-modality approach in management of cancer primary to the head and neck.

PRINCIPLES OF CLINICAL TRIALS INVOLVING CHEMOTHERAPY

Endpoints of Clinical Trials

Survival

If chemotherapy conveys clinical benefit to patients it must be shown to increase either the duration or quality of survival. Duration of survival depends on stage and grade of disease, tumor bulk and sites of involvement, performance status, and other prognostic factors, in addition to the effects of treatment. A comparison of survival curves for patients treated in nonrandomized clinical trials, therefore, does not give useful information. The only exception is the demonstration of long-term survival for a subgroup of patients with metastatic cancer of the head and neck, but with the possible exception of nasopharyngeal cancer, this does not appear to be an achievable goal. Comparison of survival is particularly important when two or more groups of patients are compared in a randomized trial, and when chemotherapy is used as part of combined-modality treatment with curative intent, survival should be regarded as the primary endpoint.

Survival should be reported for all patients entered in a clinical trial, regardless of treatment received. Most clinical trials are best designed to evaluate the policy of giving a certain treatment, and exclusion of patients after entry introduces bias. Many authors have reported cause-specific survival and have excluded deaths that are apparently unrelated to cancer, such as accidents or myocardial infarction. Patients with cancer of the head and neck often have additional medical problems, social problems, or both, that place them at higher risk of death from other causes than an age-matched population, but absolute survival should always be reported as well as cause-specific survival. Otherwise, indirect adverse ef-

fects of chemotherapy (eg, heart failure associated with fluid loading) may be excluded.

Some investigators have claimed benefit for chemotherapy by demonstrating longer survival of responding patients (those with tumor shrinkage) than for nonresponding patients. This observation almost always can be made, both in treatment of recurrent or metastatic disease and when chemotherapy has been used before surgery, irradiation, or both for locally advanced disease. It does not, however, imply a cause and effect relation.[3] Survival may, indeed, be longer in responding patients because of the effects of chemotherapy; alternatively, patients who have a better prognosis may be more likely to respond to drug treatment, and would have had better survival even in the absence of such treatment. Resolution of these alternatives can only be achieved by comparing in a randomized trial the overall survival of groups of patients who do and do not receive chemotherapy.

Quality of Life

Even if chemotherapy does not lead to detectable increases in the duration of survival, it might relieve pain and other symptoms with consequent improvement in quality of life. This is a major goal when chemotherapy is used with the intent of palliating patients with metastatic cancer. Quality of life is multidimensional, and its assessment requires the use of validated questionnaires. Such questionnaires, or *instruments*, have been developed and used for other types of malignancy,[20,46,50] but have not been incorporated into clinical trials of chemotherapy for cancer of the head and neck. Since the major aim of treatment for recurrent or metastatic disease is palliation, validated endpoints to assess palliation must be used in future trials of chemotherapy for this group of patients.

Tumor Response

Shrinkage of tumor as a result of chemotherapy is an essential prerequisite for improvements in quality or duration of survival; in contrast, the observation of tumor response cannot be assumed to convey clinical benefit, especially when treatment is associated with toxicity. The demonstration that a drug, or drugs, cause a reasonable probability of tumor response in a phase II trial thus should be regarded only as generating a hypothesis that the treatment is clinically beneficial. This hypothesis must then be evaluated by comparing the new treatment with a standard approach in a randomized trial where the appropriate endpoints are survival and quality of life.

The assessment of tumor response is subject to considerable error. To determine the magnitude of measurement error, Warr and coworkers asked several physicians to measure perpendicular diameters of cervical lymph nodes in patients within a 36-hour interval, and compared these measurements.[73] Comparison of pairs of measurements of the cross section of identical lesions showed that on about 13% of occasions the second measurement of the pair was less than 50% of the first; if determination of partial response (PR) depends only on the demonstration of 50% shrinkage in cross section between an initial and one subsequent evaluation, then measurement error alone may lead to a false rate of PR of about 13%. Considerable variability also is found in the criteria that are used to assess tumor response.[67] Whereas most investigators require a 50% shrinkage in a cross-sectional area for PR, variability exists in definition of start and end of response, frequency of measurement, number of evaluations required to determine response, and criteria for multiple lesions and for lesions that cannot be measured. These factors, as well as variable exclusion of patients, were shown to lead to large differences in the reported rate of response when criteria used by different authors were applied to a single set of data.[5,67] Comparing rates of tumor response for different series of patients, therefore, cannot be used to assess the relative merits of different drug regimens.

In general, the rates of tumor response reported in clinical trials conducted by cooperative oncology groups tend to be lower than those reported from the use of identical chemotherapy in single institutions. Although this may be due, in part, to selection of patients and better patient care by a committed group in a single institution, it also reflects the quality control that has been developed by the cooperative groups. Such quality control includes well-defined and rigorous criteria of response, inclusion of all patients, and peer review of data. Experience of these groups is likely to reflect the expected rate of tumor regression when treatments developed in a single institution are exported to the community.

Nonrandomized Clinical Trials

Randomized trials are required to provide rigorous evaluation of the clinical value of new approaches to treatment, but their size and cost provides a severe limitation on the number of new treatments that can be evaluated in this way. Nonrandomized trials, therefore, have an important place in the development of new treatments, although only in settings where there are quantum leaps in the effectiveness of new treatment can they be used as definitive evidence of improved therapeutic benefit. This is not likely to occur from chemotherapy of cancer of the head and neck. Single-arm trials, therefore, should be used to assess feasibility and to generate hypotheses about benefits of new treatments.

New agents that have demonstrated ability to kill cancer cells in tissue culture and animal models receive their initial evaluation in phase I trials. The goal of such trials is to determine a maximal tolerated dose and to assess the toxicity and pharmacokinetics of treatment. Increasing doses are administered to small groups of volunteer patients with a variety of malignant diseases for whom no standard treatment is available, and dose escalation is stopped when a certain level of toxicity is found.

Phase II trials evaluate biologic activity of new drugs or drug combinations for patients with a given type of malignant disease. For new agents, patients with cancer of the head and neck are treated at the maximum tolerated dose determined from phase I trials and the primary endpoint is tumor response. Only patients with measurable lesions, who can be evaluated for tumor response, usually are included. Traditionally, new agents have been rejected for further study if the probability of response is less than 20%; if a phase II trial demonstrates no responses among 14 patients, usually it is terminated because one can be fairly certain that the true response rate in a larger trial would not exceed 20% ($P < .05$). If more responses are found the trial usually is enlarged, or

additional phase II studies are conducted, where the new agent is used in combination with other drugs. Again, the demonstration of tumor responsiveness is not equivalent to the demonstration of clinical benefit. As stated previously, a number of factors invalidate comparisons between rates of survival or tumor response between series of patients treated in different single-arm trials. The deliberate or inadvertent selection of patients with different prognostic factors, and variability in criteria of response and quality of care, are major reasons for not comparing rates. Two additional factors are publication bias and stage migration.

Publication bias refers to the greater probability that investigators will report, and journals will publish, clinical trials that show improvements in therapy compared with those that do not.[58] This leads to bias in the published literature in favor of positive trials.

Stage migration refers to the effect of newer and more sensitive diagnostic tests to detect small deposits of disease and to move patients into a higher stage.[9,27] This effect invalidates stage-by-stage comparison with historical controls. Because patients with relatively advanced disease, formerly assigned to a given stage, may now be upstaged, the effect of stage migration may be to show an apparent improvement in each *stage* of disease, without any change in outcome for the overall population. This paradox is illustrated in Figure 7-1.

Randomized Trials

Therapeutic approaches that appear to be highly promising in phase II trials should be selected for evaluation in randomized phase III trials to assess whether they convey greater therapeutic benefit than standard treatment. When new treatments are used to palliate patients with recurrent or metastatic disease, the standard treatment might be best supportive care, or treatment with methotrexate, which can be given with limited toxicity. When chemotherapy is used with irradiation, surgery, or both, then standard treatment should be the same local–regional therapy given alone. If chemotherapy is used concurrently with irradiation, however, it often leads to increased normal tissue reactions, and it may be more appropriate to compare the combined-modality approach with a somewhat higher dose of radiation used alone, so that survival can be compared at roughly equal levels of normal tissue toxicity.

The sample size required in a randomized clinical trial depends on the difference in outcome (eg, survival at a specified time) that is to be detected or ruled out with given levels of certainty, and on the expected outcome in the control group. The probability that a measured difference in survival could have occurred by chance alone is called the type I error; the probability of the trial detecting a real difference in outcome of a specified amount is known as its power $(1 - \beta)$, where β is referred to as the type II error. Standard tables can be used to estimate sample size (eg, see Gehan and Schneiderman[30]). Detecting or ruling out a 15% difference in absolute survival at a given time of follow-up, with usual values of $P = .05$ and $1 - \beta = .90$, typically requires about 250 patients. When the population is heterogeneous, which usually is the case for cancer of the head and neck, differences in outcome among subgroups in each arm often are larger than the overall improvement in survival that can be contemplated from use of chemotherapy. This heterogeneity can be allowed for, in part, by stratification of patients by known prognostic factors. Use of more than two or three strata is not useful, however, because subgroups then are too small, and a larger sample size than that estimated from standard tables may be required to allow for differences in distribution of other known or unrecognized prognostic factors. Also, it is usual and preferable to evaluate statistically the differences between survival curves rather than survival rates at one particular time.

Few randomized trials have been performed that are large enough to detect or rule out differences in survival that might be expected to occur from chemotherapy. Most trials have been reported as showing no significant difference in outcome, but are too small to rule out differences that would be regarded as clinically important. Smaller trials can be useful if survival rates of patients in

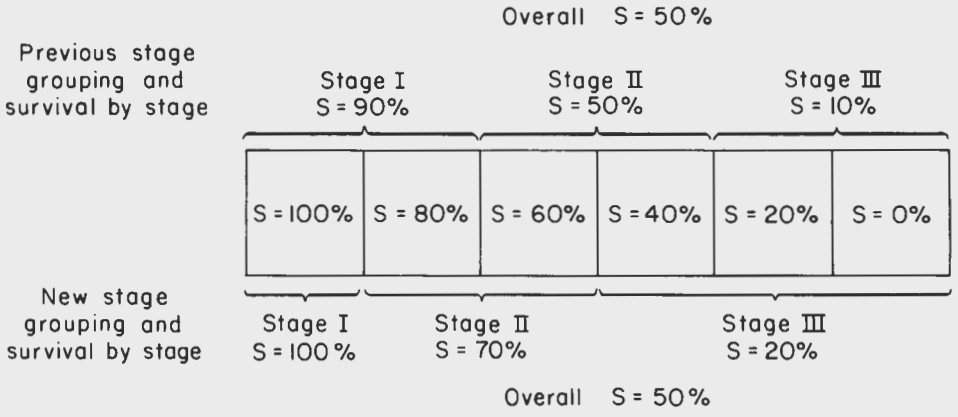
Overall S = 50%
Previous stage grouping and survival by stage
Stage I S = 90%
Stage II S = 50%
Stage III S = 10%
S = 100%
S = 80%
S = 60%
S = 40%
S = 20%
S = 0%
New stage grouping and survival by stage
Stage I S = 100%
Stage II S = 70%
Stage III S = 20%
Overall S = 50%

Figure 7-1. Stage migration. The figure indicates a hypothetical example in which patients are divided into six equal groups, within which the survival rate varies from 0% to 100%. The overall survival rate is 50%. Introduction of more sensitive staging investigations moves patients into higher stage groupings as shown, and there is an apparent improvement in survival for stages I, II, and III. The overall survival rate of 50% remains unchanged, however. (Tannock IF. Combined modality treatment with radiotherapy and chemotherapy. Radiother Oncol 1989;16:85)

the experimental arm show a nonsignificant trend to being *poorer* than for the control arm, and where confidence limits allow the exclusion of an improvement in survival of a specified amount from the experimental treatment. This has occurred in some trials where chemotherapy has been given to improve the results of irradiation, surgery, or both.[42,62,68] Relatively small trials that test similar strategies also can be combined in a metaanalysis. Differences in outcome that are not significant in individual trials may prove to be significant when the trials are combined. The method must be used cautiously, because publication bias may lead to a higher probability of inclusion of apparently positive trials, and because the overall results depend on methodologic rigor in individual trials. A metaanalysis of various types of chemotherapy used as an adjunct to irradiation, surgery, or both, for locally advanced disease, has been performed by Stell and Rawson, and is reviewed in a subsequent section.[61]

The preceding sections have indicated that meaningful improvements in therapeutic outcome must be demonstrated in large randomized clinical trials. The following review of results of chemotherapy for metastatic or recurrent disease, as part of the treatment for locally advanced disease, emphasizes this type of trial.

CHEMOTHERAPY FOR RECURRENT OR METASTATIC DISEASE

Squamous Cell Cancer

Clinical trials for squamous cell cancer usually have included a heterogeneous group of patients, and substantial differences may exist in the probability of tumor response among certain subgroups (see below). The results of some of the larger randomized trials are summarized in Table 7-1. Including patients with a variety of prognostic factors tends to lead to an "average" outcome, but even in these trials, differences in criteria for inclusion of patients will occur, and it is not valid to compare outcome measures between the different trials.

Methotrexate is the drug that has been used most extensively for treatment of cancer of the head and neck. In large cooperative group studies, treatment with intravenous doses of 40 to 60 mg/m^2/wk leads to response rates in the range of 10% to 35%, but median duration of response usually is short, about 2 to 5 months. Three studies have compared different doses of methotrexate used with or without leucovorin rescue,[17,72,77] but no trend to improvement in survival is shown when higher doses of methotrexate are used with leucovorin. Recent evidence suggests that leucovorin abrogates not only toxicity, but also antitumor effects of methotrexate.[8] A number of single agents have been reported to have activity in phase II clinical trials, but response rates generally have been equal to or lower than those reported for methotrexate, and often have been associated with more toxicity. Single agents with low but definite activity include cisplatin and bleomycin, but two randomized trials comparing methotrexate given intravenously or intramuscularly in conventional doses with intravenous cisplatin (50 mg/m^2 on days 1 and 8 of a 4-week cycle) found either lower or equivalent response rates for cisplatin, and remissions were short.[32,35] In two British trials, patients were randomized to cisplatin alone or with another drug, bleomycin alone (first trial only), methotrexate alone at a low dosage (second trial only), or a no-chemotherapy arm (first trial only).[10,51] Not all patients who were randomized to receive chemotherapy received their drugs, but the groups were compared on the basis of intended treatment. In both trials, survival rates were higher for patients assigned to receive cisplatin (alone or with other drugs), but both the number of treated patients in each arm and the reported differences in survival were small; also, the statistical analysis was suspect because of failure to correct for multiple comparisons between the groups.

Single-agent methotrexate has been compared with drug combinations in four large cooperative group trials (see Table 7-1). Cisplatin-based combination chemotherapy was shown to give a higher response rate in two large randomized trials: 48% for methotrexate, bleomycin, and cisplatin versus 35% for methotrexate alone in an Eastern Cooperative Oncology Group trial[71]; and 32% for cisplatin and 5-fluorouracil (5FU) by infusion versus 10% for methotrexate alone in a Southwest Oncology Group study.[28] Unfortunately, the increased rate of response with combination chemotherapy was not associated with improved survival rates in either trial, but combination chemotherapy was associated with greater toxicity. Neither trial included a formal assessment of quality of life, but it seems unlikely that available drug combinations convey increased therapeutic benefit compared with methotrexate alone. Moreover, the infrequent responses and their short duration in these trials suggest that these patients might have been managed as effectively with supportive care, although this has not been tested formally in a large study.

The clinical trials summarized in Table 7-1 have included a heterogeneous group of patients, and they might conceal the presence of small subgroups who derive greater benefit from treatment. The dominant factors that tend to increase the probability of response to chemotherapy are a high performance status of the patient,[2,31,71] lack of prior treatment with irradiation or surgery, absence of fixed nodes, and a nasopharyngeal primary tumor. One group of patients who should be offered chemotherapy routinely are those with metastatic or recurrent undifferentiated tumors of the nasopharynx. These patients have disease that may be associated with prior exposure to the Epstein-Barr virus, and usually are young or middle aged, without other underlying medical or social problems. The disease has a high incidence in people in or from China and southeast Asia, and from countries bordering on the Mediterranean sea. Chemotherapy incorporating cisplatin with other drugs, such as bleomycin, doxorubicin, or both, has a high probability of leading to response, and a small proportion of such patients have complete responses that are sustained for at least 3 years.[7,12] Further trials with longer follow-up are required to determine whether a small subset of these patients may be cured by chemotherapy.

With the exception of small subgroups of patients such as those with poorly differentiated tumors of the nasopharynx, the current data indicate a limited role for chemotherapy in palliation of recurrent or metastatic squamous cell cancer of the head and neck. Chemotherapy should not be regarded as part of standard management and most patients who wish to undergo a trial of drug treatment should be encouraged to take part in phase II trials that evaluate new agents.

TABLE 7-1. Larger Randomized Trials That Have Evaluated Chemotherapy for Patients With Recurrent or Metastatic Squamous Cell Cancer of the Head and Neck

References*	Drug Regimen†	Patients	Response Rate (%)	Median Duration (mo)	Survival
SECSG (Vogler et al,[72] 1979)	Methotrexate (weekly × 12)	154		Not stated	No difference
	500 mg/m² PO + leucovorin		22		
	60 mg/m² PO		27		
	60 mg/m² IV		31		
Woods et al,[77] (1981)	Methotrexate + leucovorin (weekly)	72			No difference; greater toxicity with highest dose
	5 g/m²		45	4	
	500 mg/m²		26	2	
	50 mg/m²		26	1.5	
ECOG (De Conti and Schoenfeld,[17] 1981)	Methotrexate (40–60 mg/m² weekly)	237	26	3	Favored low-dose methotrexate
	Methotrexate (240 mg/m² every 2 wk) and leucovorin		24	1.5	
	Methotrexate, cyclophosphamide, and Ara-C		18	1.5	
SWOG (Grose et al,[32] 1985)	Methotrexate (15 mg/m² IM for 3 d every 3 wk)	100	16	4.5	No difference
	Cisplatin (50 mg/m² on days 1 and 8 every 4 wk)		8	2	
NCOG (Jacobs et al,[37] 1983)	Cisplatin (80 mg/m² every 3 wk)	79	18	7	No difference
	Cisplatin + methotrexate (250 mg/m² weekly) + leucovorin		33	4	
SECSG (Williams et al,[75] 1986)	Methotrexate (45–60 mg/m² weekly)	190	16	5	No difference
	Cisplatin, vinblastine, bleomycin		24	4	
ECOG (Vogl et al,[71] 1985)	Methotrexate (40–60 mg/m² weekly)	163	35‡	4	No difference
	Methotrexate, cisplatin, bleomycin		48	5	
Morton et al,[51] (1985)	No chemotherapy	116	—	Not stated	Trend to improved survival in cisplatin arms
	Bleomycin (15 mg/d for 5 d, monthly)		14		
	Cisplatin (100 mg/m² monthly)		13		
	Bleomycin + cisplatin		24		
Campbell et al,[10] (1987)	Methotrexate (40 mg/m² every 2 wk)	124	19	Not stated	Favors cisplatin arms
	Cisplatin (100 mg/m² monthly)		40		
	Cisplatin + methotrexate		31		
	Cisplatin + 5FU (1 g/m² for 4 d monthly)		33		
EORTC (Clavel et al,[15] 1987)	Methotrexate, bleomycin, vincristine	185	28	4	No difference
	Same + cisplatin		50‡	7	
Jacobs et al,[36] (1992)	Cisplatin (100 mg/m² every 3 wk)	249	17	Not stated	No difference
	5FU (1 g/m² for 4 d every 3 wk)		13		
	Cisplatin + 5FU		32‡		
SWOG (Forastiere et al,[28] 1992)	Methotrexate (40–50 mg/m² weekly)	277	11	4	No difference
	Cisplatin (100 mg/m²) + 5FU (1 g/m² for 4 d), every 3 wk		30‡	5	
	Carboplatin (300–360 mg/m²) + 5FU, every 4 wk		18	5	

Ara-C, cytarabine; PO, by mouth; IV, intravenously; IM, intramuscularly; 5FU, 5-fluorouracil.

* Cooperative groups are ECOG, Eastern Cooperative Oncology Group; EORTC, European Organization for Research and Treatment of Cancer; NCOG, Northern California Oncology Group; SECSG, Southeastern Cancer Study Group; SWOG, Southwestern Oncology Group.

† Drugs were given intravenously unless otherwise stated.

‡ Differences in response rate between two of the arms were significant at $P < .05$ in these four studies. There were no significant differences in response rate in other trials.

Tumors of the Salivary Glands

Most tumors originating in the head and neck are squamous cell carcinomas, but a lower incidence of tumors with a variety of different histologic types exists, including lymphomas, sarcomas, and tumors originating in major or minor salivary glands. Although uncommon, these tumors occur in young or middle-aged people, and have a higher probability of metastasis to the lungs and elsewhere than squamous cell carcinomas.

Experience with chemotherapy is limited for metastatic tumors of the salivary glands. In a review of the

literature and a survey of various institutions, Suen and Johns collected data on 85 patients who had been treated with chemotherapy, and reported an overall response rate of 42% with 10% clinical complete remissions.[63] This rate of response is subject to the problems associated with a retrospective review, and may be regarded as an upper limit of what might be reported if a similar group of patients were treated in a rigorously conducted prospective trial; it indicates, however, that some patients have tumors that are responsive to chemotherapy. The majority of patients in this review had adenoid cystic carcinoma (53 of 85) with small numbers in each of the other subtypes; responses were observed among patients with each histologic subtype, but numbers are too small to indicate trends in responsiveness. Small individual series have reported a consistent rate of response (36% to 46%) to cisplatin-based chemotherapy.[16,21,69]

Many patients with salivary gland tumors develop slowly growing pulmonary metastases that may remain asymptomatic for months, or even years. These patients should be observed. For symptomatic patients it is reasonable to offer a trial of palliative chemotherapy using a cisplatin-containing drug regimen.

CHEMOTHERAPY USED AS AN ADJUNCT TO SURGERY AND RADIATION THERAPY

Clinical trials have investigated the use of chemotherapy before surgery or radiation therapy (known as induction or neoadjuvant chemotherapy), concurrent with radiation therapy, or for patients at high risk of recurrence who have no evidence of disease after local treatment with radiation therapy or surgery (adjuvant chemotherapy), as shown in Figure 7-2. The major aim of the various types of adjunctive chemotherapy is to improve survival rates, but mechanisms are likely to be different from those that have allowed improved survival rates in premenopausal women with breast cancer, or in young patients with osteogenic sarcoma. In those diseases, a high rate of failure in distant metastatic sites occurs, and adjuvant chemotherapy exerts its therapeutic effect through eradication of occult metastases. Distant metastases occur rarely in cancer of the head and neck in the absence of local or nodal recurrence[48] (Table 7-2). Even if chemotherapy reduced the rate of metastatic failure to zero, it would take large trials to detect an improvement in overall survival, with the possible exception of trials for nasopharynx tumors, where metastatic failure is more common. If adjunctive chemotherapy is to improve survival rates of patients with cancer of the head and neck, it must complement the effects of surgery and irradiation to increase the probability of disease control in the primary site and in the neck.

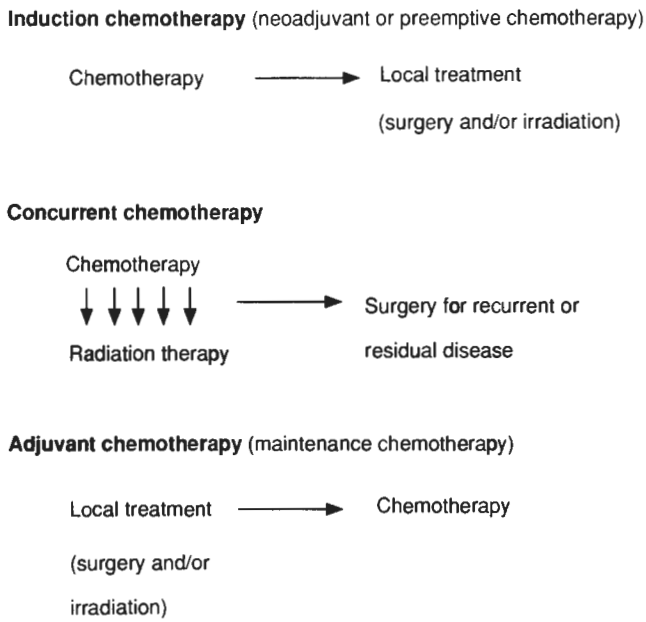

Figure 7-2. Various types of adjunctive chemotherapy that have been used in the treatment of locally advanced head and neck cancer. Combinations of these approaches have been tested in some clinical trials.

TABLE 7-2. Percentage of Patients with Head and Neck Cancer Who Relapse Only in Distant Sites

	Patients	Distant Relapse Only (%)
Oral cavity	1710	1.8
Oropharynx	1098	6.6
Nasopharynx	224	17.4
Paranasal sinus or nasal cavity	230	3.0
Supraglottic larynx	466	9.2
Vocal cord	858	0.8
Hypopharnyx	433	14.5
All T1–2	2516	3.6
T3–4	2503	6.8
All N0	3004	1.6
N+	2015	10.6

(Adapted from Merino OR, Lindberg RD, Fletcher GH. An analysis of distant metastases from squamous cell carcinoma of the upper respiratory and digestive tracts. Cancer 1977;40:150)

The following sections review the results of randomized clinical trials that have evaluated the role of chemotherapy in each of the sequences shown in Figure 7-2, together with aspects of tumor biology that relate to the use of such treatment.

Induction Chemotherapy

When patients with locally advanced cancer of the head and neck receive initial treatment with chemotherapy, the probability of tumor response is higher than for patients who have recurrent or metastatic disease after completion of local therapy. Reports from single institutions have indicated response rates of 70% to 90%, with complete clinical responses of 20% to 50% when patients have been treated with aggressive cisplatin-based regimens.[22,23] Up to 40% of patients who achieve clinical complete response have no detectable tumor in surgical specimens after resection of the previously involved area.[1] Patients who have a good response to chemotherapy almost invariably have a better prognosis than those who do not respond. These results do not prove the value of chemotherapy, but they encourage the belief that chemotherapy increases the probability of cure. They have

unfortunately led to the widespread use of induction chemotherapy outside the setting of clinical trials, which offer the only method for evaluating the long-term effects of such treatment.

Results of randomized, controlled clinical trials that have evaluated the results of induction chemotherapy are summarized in Table 7-3. The initial rate of complete response to chemotherapy evidently is lower than that reported from single institutions, even in recent trials where aggressive chemotherapy has been used. This may reflect selection of patients, the higher intensity of treatment, or both, that may result from the care of a committed team. Many of the trials have methodologic limitations, such as exclusion of patients after randomization; some have been reported only in abstract form; and some have follow-up that is too short to be definitive. Most are too small to detect clinically relevant differences in survival.[14] Despite these limitations, the results are disappointing: no overall trend is shown for improvement in survival rates among patients who were randomized to receive induction chemotherapy.

Many of the trials that are summarized in Table 7-3 used chemotherapy that is now considered to be suboptimal. More recent trials have evaluated the use of aggressive regimens such as 5FU and cisplatin by infusion, or other cisplatin-based regimens that were associated with considerable toxicity. One of these trials was discontinued after entry of only 60 patients, because of a trend to poorer survival in patients receiving chemotherapy; in this trial, and in two others with similar trends, the authors were able to exclude a beneficial effect of chemotherapy on survival, and raised concerns about delay in initiation of effective local treatment.[62,68] Other trials that have evaluated the role of several courses of cisplatin-based chemotherapy have not indicated any consistent trends toward improvement in the probability of tumor clearance or survival in patients randomized to receive induction chemotherapy.

The metaanalysis of trials of induction chemotherapy undertaken by Stell and Rawson[61] involved pooling of results from publications describing many of the trials that are summarized in Table 7-3. The overall ratio of

TABLE 7-3. Larger Randomized Controlled Trials That Have Evaluated the Role of Induction Chemotherapy in Treatment of Patients With Locally Advanced Cancer of the Head and Neck

Authors	Patients	Follow-Up (Years)	Type of Chemotherapy	Response to Chemotherapy		Influence on Survival
				Total (CR + PR)	Complete (CR)	
Knowlton et ol,[41] (1975)	96	5	Methotrexate	NS	NS	No difference
Fazekas et al,[26] (1980)	638	5	Methotrexate	NS	NS	No difference (favors chemotherapy)
Stell et al,[62] (1983)	86	2.5	Seven drugs (2 cycles)	NS	NS	No difference (favors control arm)
Arcangeli et al,[4] (1983)	142	5	Intraarterial methotrexate	NS	NS	Improved survival with chemotherapy ($P < .05$)
Taylor et al,[66] (1985)*	82	3	Methotrexate + leucovorin (1 cycle)	40	6	No difference
Kun et al,[42] (1986)	83	3	Bleomycin methotrexate, 5FU (2 cycles)	68	5	No differences (favors control arm)
Head and Neck Contracts Program[34] (1987)*	462	5	Cisplatin bleomycin, (1 cycle)	37	3	No difference
SWOG (Schuller et al,[56] 1988)	158	5	Cisplatin, methotrexate, bleomycin, vincristine (3 cycles)	70	19	No difference (favors control arm)
Carugati et al,[11] (1988)†	120	5	Cisplatin, bleomycin + methotrexate	52	NS	No difference (favors chemotherapy)
Martin et al,[47] (1988)†	107	2	Cisplatin, 5FU, bleomycin, methotrexate	49	6	Too early (disease-free survival favors control arm)
Paccagnella et al,[53] (1990)†	221	1–3	Cisplatin/5FU (4 cycles)	70	16	Too early (no difference in tumor clearance)
Jaulerry et al,[38] (1992)	100	5	Cisplatin, 5FU, vindesine, mitomycin C (2 cycles)	50	10	No difference
Jaulerry et al,[38] (1992)	108	2.5	Cisplatin, 5FU, vindesine (3 cycles)	70	22	No difference

NS, not stated; CR, complete response; PR, partial response; SWOG, Southwest Oncology Group; 5FU, 5-fluorouracil.

* All or some of the patients randomized to receive chemotherapy were also scheduled to receive adjuvant chemotherapy after local treatment.

† Reported only in abstract form.

rates of survival for patients randomized to receive induction chemotherapy compared with controls was 0.92 ± 0.11, a nonsignificant trend toward harmful effects of chemotherapy. This analysis also suggested no trend for patients to fare better after aggressive multiagent chemotherapy, although as stressed earlier, metaanalysis may be confounded by methodologic problems leading to bias in individual trials. Bias tends to operate in favor of experimental treatment, however. Neither individual trials nor the metaanalysis suggests therapeutic benefit from induction chemotherapy.

A randomized trial that does not involve a simple comparison of induction chemotherapy versus a control group was undertaken by the Department of Veterans Affairs Laryngeal Cancer Study Group (VA) in patients with advanced larynx cancer.[18] The design of this trial is illustrated in Figure 7-3. The results demonstrated equivalent survival in the two arms, with 64% of patients in the chemotherapy arm alive and well with an intact larynx. This trial has been interpreted as providing evidence for the value of chemotherapy in allowing laryngeal preservation. This conclusion cannot be justified, however, because randomized controlled studies have shown equivalence of disease control and survival rates for patients treated with radiation therapy alone, or induction chemotherapy followed by radiation therapy (see Table 7-3). Thus, patients treated in the chemotherapy arm of the VA study might have fared as well with a policy of using only primary irradiation with surgery reserved for salvage of residual or recurrent disease (as is performed in many Canadian and European centers). An important new study has been planned in which patients with advanced laryngeal cancer will be randomly assigned to recieve chemotherapy followed by radiation therapy (as in the VA trial), radiation therapy alone, or radiation therapy with concurrent cisplatin therapy, with strict guidelines for surgery if there is no response or if the disease persists.

Biologic Basis for Limitations of Induction Chemotherapy

The ability of induction chemotherapy to induce shrinkage of a tumor in a high proportion of patients with cancer of the head and neck, with no evidence for improvement in survival, is a disappointing enigma. Possible reasons for these discordant results on tumor response and survival follow.

Inadequate Cell Kill

A large tumor of the head and neck may weigh 10 to 100 g and contain 10^{10} to 10^{11} tumor cells. Reduction in cell number by chemotherapy to $\sim 10^9$ cells ($\sim$1 g of tumor) would be regarded as a good PR, and a residual cell number of 10^8 cells ($\sim$0.1 g) probably would escape clinical or radiologic detection and be assessed as a complete response. Because given doses of drugs and radiation tend to kill a given fraction of tumor cells, rather than a given number, leading to exponential cell survival curves, this visually impressive tumor response is a small step toward cure[64,65] (Fig. 7-4). Even a pathologically confirmed complete response may be consistent with the presence of $\sim 10^6$ viable tumor cells per gram of tissue, since it is unlikely that a pathologist can detect tumor cells that are dispersed among normal cells at a frequency of 1 in 1000 or less. Attaining tumor response after induction chemotherapy, therefore, may be consistent with a limited cell kill, a premise that is supported further by the short median duration of response that is observed after treatment of patients who do not go on to receive irradiation or surgery.

If the effects of chemotherapy are additive with those of irradiation and surgery, it remains to be explained, however, why drug effects do not at least contribute to improved survival rates.

Reduction in Surgical or Radiation Fields After Chemotherapy

Limited cell kill after tumor response to chemotherapy suggests that any anatomic region that is grossly involved with tumor at initiation of chemotherapy is likely to contain residual viable tumor cells, even if these are not evident by physical, radiologic, or even pathologic examination. Chemotherapy does not render an unresectable tumor operable for cure, therefore, and irradiation or surgical fields should encompass all areas of disease that were present before chemotherapy. Most clinical trials have stipulated this requirement, but particularly in multiinstitution trials, it may be difficult to

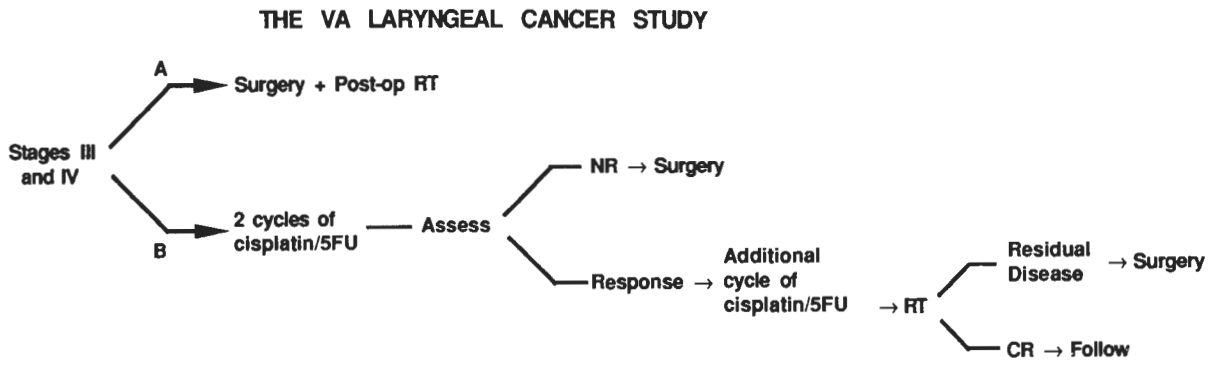

Figure 7-3. Design of the Veterans Administration Laryngeal Cancer Study Group Trial. Early results of the study show equivalent survival rates in the two arms, with about 60% of patients in arm B surviving with larynx intact. Failure of induction chemotherapy to improve survival in other studies (see Table 7-3), however, suggests that similar results might have been obtained in arm B by using initial radiation therapy alone.

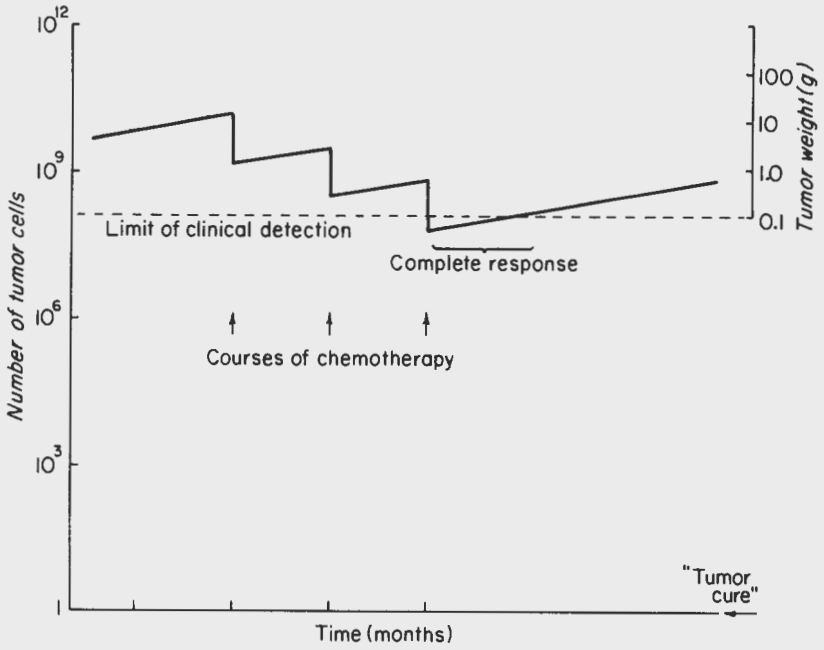

Figure 7-4. A hypothetical tumor containing 10^{10} viable cells (about 10 g) is treated with three courses of chemotherapy, each of which kills 90% of the cells. There is some repopulation between treatments. After three courses, the number of viable tumor cells is less than 10^{8} (about 0.1 g), and the patient is judged to be in complete clinical and radiologic remission. This is a small step toward tumor cure. Also, additional chemotherapy may not be helpful if drug-resistant cells have been selected after three courses of chemotherapy. (Tannock IF. Combined modality treatment with radiotherapy and chemotherapy. Radiother Oncol 1989;16:94)

ensure rigid adherence to this criterion. It is unlikely that reduction in the extent of local–regional therapy has been a major contributing factor in the disappointing results that have been observed after induction chemotherapy.

Reduction in Response to Radiation After Chemotherapy

Large tumors tend to be poorly vascularized, leading to regions of necrosis, as well as nutrient-deprived regions where the rate of cell proliferation is low. Shrinkage of tumor after chemotherapy might lead to improved vascularity. This can have opposing effects on subsequent response to irradiation: improvement in oxygenation would tend to increase responsiveness to irradiation, whereas an effect to induce more rapid proliferation of surviving tumor cells would be detrimental, as illustrated schematically in Figure 7-5.[64] Although no direct evidence exists for an effect of chemotherapy-induced shrinkage to stimulate proliferation in human tumors, this effect has been found to occur in tumors of rats and mice. It also is supported by the finding that when irradiation is used alone as the primary treatment for cancer of the head and neck, radiation dose must be increased if the duration of fractionation is prolonged beyond about 4 weeks, presumably because of increased proliferation of tumor cells after this time.[76] This observation suggests that the detrimental effects on radiation response from stimulation of tumor cell proliferation may outweigh any beneficial effects due to reduction in hypoxic function. Prior exposure to chemotherapy has been reported by some investigators to cause a decrease in the intrinsic radiosensitivity of cells.[45] This effect has been described after treatment with alkylating agents, cisplatin, and doxorubicin, but the effects are inconsistent and vary with the cell lines that have been studied. One possible mechanism may be drug-induced stimulation of glutathione synthesis, or induction of the enzymes glutathione-S-transferase and glutathione reductase, which are involved in the inactivation of radical species that are produced by some anti-cancer drugs as well as by ionizing radiation.[13] Direct investigation of the radiosensitivity of cells in tumors of the head and neck after initial chemotherapy would provide useful information about common mechanisms of therapeutic resistance.

Concurrent Treatment With Radiotherapy and Chemotherapy

Randomized controlled trials that have evaluated the role of concurrent radiotherapy and chemotherapy (with or without surgery) are summarized in Table 7-4. An additional trial from China showed improved disease-free survival for patients randomized to receive a Chinese herb concurrent with irradiation for nasopharyngeal cancer, compared with irradiation alone.[78] Most of the trials summarized in Table 7-4 do not show significant differences in survival, but several of them show trends to improvement in local control, survival, or both. These trends have been observed for concurrent treatment with bleomycin, cisplatin, 5FU, and mitomycin C, and most often have been observed for tumors of the oral cavity and oropharynx. An Italian trial has also shown a small but significant improvement in survival from the use of alternating courses of chemotherapy (cisplatin and 5FU) and radiation therapy, as compared with conventional radiation therapy alone.[49] Most of the trials have reported an increase in acute toxicity from use of chemotherapy, and there has been no evidence of reduction in metastatic failure.

Although the results summarized in Table 7-4 are encouraging, they do not provide definitive evidence for therapeutic benefit from chemotherapy. All but one of the trials compared treatment with the same irradiation dose and schedule as for radiation therapy used alone. An effect to increase local control at the expense of greater normal tissue reactions might have been achieved by using a higher dose of radiation without

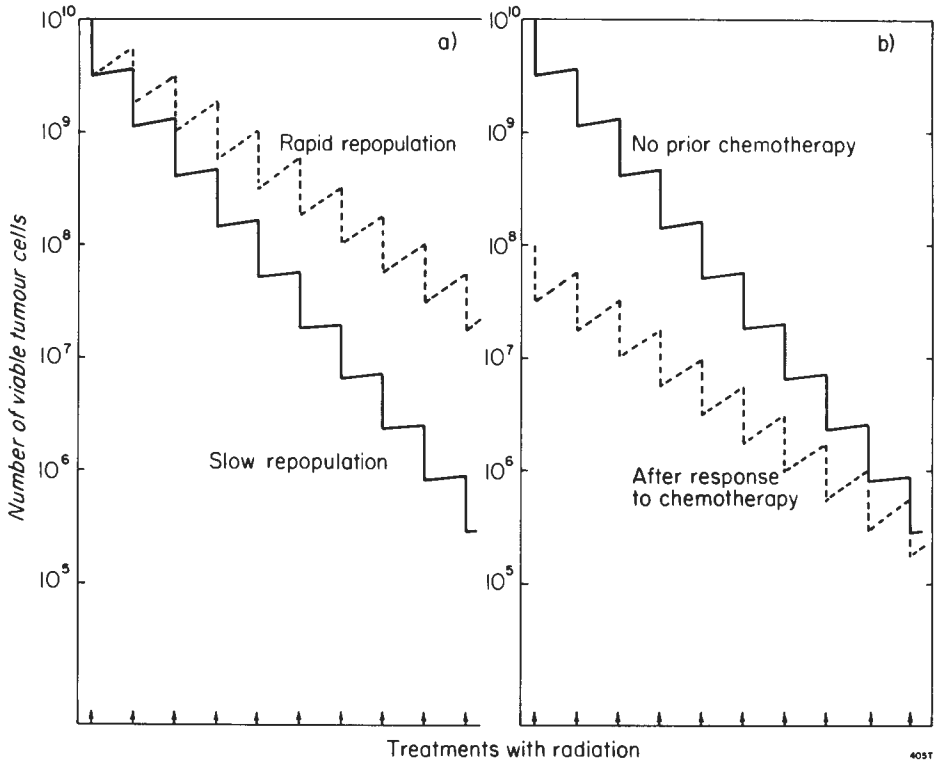

Figure 7-5. (*A*) Schematic illustration of the effect of cell proliferation between dose fractions on cell survival after fractionated radiation. The two curves are drawn with the same cell kill from each dose fraction but with differing rates of repopulation between dose fractions. (*B*) Solid curve indicates the expected survival of tumor cells during fractionated radiation therapy given to a previously untreated tumor. Dashed curve reflects the expected survival of tumor cells for radiation therapy given after induction chemotherapy if drug treatment leads to stimulation of cell proliferation after initial tumor response. There is no gain from combined treatment at the end of the course of radiation. (Tannock IF. Combined modality treatment with radiotherapy and chemotherapy. Radiother Oncol 1989;16:96)

TABLE 7-4. Larger Randomized Controlled Trials That Have Compared Radiation and Concurrent Chemotherapy With Radiation Alone for Primary Head and Neck Cancer

Authors	Patients	Follow-Up (Years)	Type of Chemotherapy	Influence of Chemotherapy
Stefani et al,[59,60] (1971, 1980)	150	10	Hydroxyurea	Poorer survival with chemotherapy ($P < .05$)
Lo et al,[44] (1976)	151	2–13	5FU	Local control and survival improved for oral cavity ($P < .05$); increased mucosal reactions
Shanta and Krishnamurthi[57] (1980)	157	5	Bleomycin	Oral cavity only; marked improvement in local control and survival ($P < .001$); increased mucosal reactions
Vermund et al,[70] (1985)	222	3–6	Bleomycin	No difference in local control or survival; increased morbidity
Fu et al,[29] (1987)	104	5	Bleomycin	Improved local control and trend to improved survival; increased morbidity
EORTC (Eschwege et al,[25] 1988)	199	10	Bleomycin	No difference in local control or survival; increased morbidity
Gupta et al,[33] (1987)	318	3	Methotrexate	Improved disease-free survival; improved survival for oropharynx cancer
Weissburg et al,[74] (1989)	120	5	Mitomycin C	Trend to improved disease-free survival; no difference in survival; increased morbidity
Keane et al,[39] (1988)*	212	1.5–6	Mitomycin C + 5FU†	No significant difference in any endpoint
Bachaud et al,[6] (1991)	83	2	Cisplatin	Improved local control and disease-free survival
Merlano et al,[49] (1992)	157	3	Cisplatin + 5FU	Improved survival ($p < 0.05$) with chemotherapy

5FU, fluorouracil; EORTC, European Orgonizotion for Research and Treatment of Cancer.
* Published in abstract form only.
† Split-course irradiation in chemotherapy arm only.

chemotherapy. In the trial where conventional radiation therapy was compared with a split course of treatment (leading to a lower effective dose) used with mitomycin C and 5FU, both survival and acute normal-tissue reactions were equivalent.[39] Few of the trials have analyzed late reactions in normal tissues that limit radiation dose. If chemotherapy has minimal effects to increase such reactions, it may, indeed, convey therapeutic benefit. Further trials should be performed where radiation dose is adjusted in the control arm to allow comparison of survival at equivalent levels of dose-limiting normal tissue toxicity.

Any beneficial effects of concurrent chemotherapy and radiation therapy may be due to added toxic effects of the two modalities, with less than additive effects against dose-limiting normal tissues. One mechanism might involve inhibition by drugs of cell proliferation, which may be stimulated in the tumor as shrinkage is accompanied by improved vascularity. This effect would lower the effective number of target cells to be killed by radiation therapy (compare with Fig. 7-5); similar effects may occur, however, in the surrounding mucosa.

It has been proposed that mitomycin C, which requires bioreduction for activity, may be beneficial because of selective effects against hypoxic tumor cells that are resistant to radiation.[74] Whereas selective toxicity of mitomycin C has been demonstrated against hypoxic cells in culture,[40] other effects such as limited penetration of the drug from tumor blood vessels have prevented the demonstration of selective killing of hypoxic cells in solid tumors of rodents.[54]

Chemotherapy Given After Radiation or Surgery

Only two large randomized controlled trials have evaluated the effects of chemotherapy administered after completion of local–regional treatment for cancer of the head and neck, and one trial has investigated the effect of the immune modulator levamisole (Table 7-5). Two of these trials show no difference in survival rates, and the other reports better survival in the control arm.[19,55] A major conclusion of these and other smaller trials is that it is difficult to administer chemotherapy to a substantial proportion of patients after radiotherapy, surgery, or both. Reasons for noncompliance include greater toxicity of the drugs when given after local treatment, especially in causing mucositis after radiotherapy, and lack of motivation in patients who have no clinically evident disease.

A large intergroup study was reported in which patients were randomly assigned to receive three courses of cisplatin and 5FU chemotherapy after complete resection of disease and before radiation therapy, or standard surgery and postoperative radiation therapy.[43] There was no difference in survival, but patients who received chemotherapy had a lower incidence of distant metastasis.

A few trials of induction or concurrent chemotherapy have included a policy of also giving adjuvant chemotherapy. The Head and Neck Contracts Program was designed as a three-arm trial in which patients received local–regional treatment only, induction chemotherapy (one course of bleomycin and cisplatin), and induction plus maintenance chemotherapy with cisplatin for 6 months.[34] There were no differences in survival, and there was poor compliance with maintenance chemotherapy: 9% of patients completed six cycles, and 27% completed three or more cycles. There was, however, a decrease in the incidence of distant failure for patients assigned to maintenance chemotherapy after local treatment. In another study, all patients received induction chemotherapy with cisplatin, bleomycin, and methotrexate, and those who had responded to chemotherapy and had no evident disease after local treatment were randomized to receive adjuvant chemotherapy or to be observed.[24] Although 144 patients were entered into the trial, a subset of only 46 patients could be randomized. The group receiving adjuvant chemotherapy had better survival rates. In view of the disappointing results of induction chemotherapy in randomized trials (see Table 7-3), it is difficult to justify the policy of using such treatment, even if it is confirmed in larger trials that a subset

TABLE 7-5. Three Randomized Controlled Trials That Have Evaluated the Results of Adjuvant Systemic Therapy Given After Locoregional Treatment for Cancer of the Head and Neck

Trial	No. of Patients	Follow-Up (Yr)	Type of Systemic Therapy	Result
Olivari et al,[52] (1979)	134	3	Levamisole	No difference in survival; increased recurrence in stage I and III patients receiving levamisole
Rossi et al,[55] (1988)	229	4	Vincristine, cyclophosphamide, doxorubicin for 6 mo	Nasopharynx cancer only; no difference in survival
Domenge et al,[19] (1988)*	287	3	Cisplatin (for 3 cycles), methotrexote, bleomycin (for 8 cycles)	Better survival in control arm ($P < .03$)

* Published only in abstract form.

of responding patients derive benefit from continuation of chemotherapy after irradiation, surgery, or both.

SUMMARY

The results of chemotherapy for all stages of cancer of the head and neck remain disappointing, and this modality should not be regarded as part of standard management. Selected patients with recurrent or metastatic disease (especially those with anaplastic tumors of the nasopharynx) may deserve a trial of cisplatin-based chemotherapy, but most patients either should be managed with supportive care, or encouraged to take part in phase II trials which evaluate new agents. No established role exists for chemotherapy as an adjunct to surgery, irradiation, or both for treatment of locally advanced disease, and it should not be used outside the setting of a clinical trial. Trials of induction chemotherapy have shown no trends to improve survival, and the most promising results have occurred in trials where radiation and drugs are administered concurrently. Randomized controlled trials should continue to evaluate chemotherapy used in this way, whereas other studies should seek to elucidate biologic mechanisms that influence the combined effects of drug treatment and local treatment with radiation or surgery.

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18

FLAPS AND GRAFTS FOR RECONSTRUCTION

SCOTT P. STRINGER

Surgical resection for head and neck cancer is considered successful and cure may result only when negative surgical margins are obtained. The limits of resection are defined largely by the resultant functional and cosmetic status of patients. In this setting, proper reconstruction is essential to enhance curability through restoration of function and form. Many reconstructive techniques are available, and the appropriate selection must be based on the surgical defect and on the individual patient's characteristics. Familiarity with multiple reconstructive techniques facilitates the optimal functional and aesthetic result.

FLAPS

Flaps differ from grafts in that they do not depend on the recipient site initially for blood supply; instead, the vascularity is maintained or surgically reestablished immediately. Flaps are further characterized according to the vascular anatomy, the location of the donor site, and whether the vascular pedicle is left intact.

Random flaps have no defined vascular pedicle but rather depend on the dermal–subdermal vascular plexus. The length of viable flap available is determined solely by the perfusion pressures in this plexus. Fortunately, the most common area in which random pattern flaps are used is the face, which has an excellent subdermal vascular plexus. This allows flaps with length/width ratios of up to 5:1 to be used for reconstruction of facial defects. Axial-pattern flaps have a known artery and vein along their long axis, and the only limitation to length of the flap is the length of the vessels. Most distant flaps fit into this pattern, particularly the musculocutaneous flaps.

Pedicled Flaps

Local

Most local flaps are developed on the face and employed for the reconstruction of skin defects after the excision of basal or squamous cell carcinomas. When possible, the lesion should be excised in a fusiform fashion and the defect closed primarily. This is especially effective when the line of excision can be placed in a crease on the cheek or forehead. More tissue is frequently needed to close the defect to prevent undue tension on the closure, however. In this situation, local random pattern flaps are most appropriate. A few of the more commonly used flaps are described.

Advancement flaps accomplish closure of defects by bringing surrounding tissue in a straight line directly into the wound. This movement is obtained by the use of releasing incisions and significant undermining of the flap. Burow's triangle excisions are sometimes required to prevent the formation of "dog ears". The advancing tissue may be brought in from one or both sides of the defect as required. Examples of unilateral advancement flaps include V-to-Y and Y-to-V closures. These flaps are used infrequently in the head and neck owing to their limited flexibility. The most common use of a bilateral advancement flap is for closure of midline forehead excisions or upper lip defects. A rotation flap entails moving contiguous skin into the defect around a fixed pivot point. Flaps of this variety are useful for closure of cheek, lower eyelid, and upper lip defects.

A transposition or interposition flap is raised from its bed and rotated over or under intervening tissue into the recipient site. These flaps are flexible, providing tissue of various sizes to close like-sized defects, while camouflaging both the donor and recipient site incisions. The Z-

plasty flap, commonly used in scar revision, is really a transposition flap and is useful in closing facial defects. The nasolabial flap is based either superiorly or inferiorly and then transposed, typically into defects of the upper lip or nose. The donor site incision is nicely hidden in the nasolabial crease. Bilobed interposition flaps are useful for closures of the cheek, especially in elderly patients with lax skin (Fig. 8-1). One of the most versatile transposition flaps for closure of small facial defects is the rhomboid because of the easy primary closure of the donor site. Additionally, the donor site may be positioned to place the incision in a relaxed skin tension line.

Regional

Regional flaps differ from local flaps in that they are brought in for closure from the same region but not from the area immediately contiguous to the defect. The flaps may have either a random or axial vascular pattern.

The cheek–neck flap is a random pattern, regional rotation flap. It is most commonly used in the closure of large lateral nasal, cheek, or lower eyelid defects. The flap is undermined below the subcutaneous fat but superficial to the facial nerve branches down into the upper neck. Closure of the donor site depends on laxity of the surrounding skin and cheating on the suture line.

Nape of neck or posterior cervical flaps are superiorly based, at least partly, on the occipital artery (Fig. 8-2). They are then rotated anteriorly for coverage of large lower facial or cervical skin defects. The disadvantages include the bulkiness of the flap, the need for skin grafting of the donor area, and the limited arc of rotation.

The midline forehead flap is an extremely reliable, axial pattern, regional transposition flap. Based on the supratrochlear vessels, it finds its greatest use in reconstruction of large nasal defects. The donor site is closed with bilateral forehead advancement sites. One disadvantage of this flap is that for more distal nasal defects, the pedicle must be divided and inset again 3 weeks after the initial procedure.

Before the advent of musculocutaneous flaps, the forehead flap was used frequently for reconstruction of oral cavity defects. Now its use is limited to reconstruction of certain large midface defects. The forehead flap utilizes the entire skin of the forehead; it is based unilaterally on the superficial temporal and posterior auricular arteries. Several disadvantages are associated with the use of this flap. The donor site requires grafting, which creates a significant cosmetic deformity. Furthermore, large forehead flaps are more reliable if rotation is delayed for 2 weeks after elevation, requiring a second procedure.

Distant

Flaps brought in from outside the region are referred to as *distant*. Most commonly, distant flaps are musculocutaneous flaps; cutaneous and osseous flaps are discussed as well, however. As operative sophistication increases, the amount of primary tissue resection increases. The musculocutaneous flap provides a reasonable, functional, and often, a satisfactory cosmetic result to patients undergoing resection. Epidermal coverage of internal or external defects is obtained with a cutaneous portion of the musculocutaneous flap, whereas the underlying muscle fills empty spaces and covers exposed vessels after large resections. The excellent pedicled blood supply of the pectoralis major muscle provides a durable flap for even the surgeon who only occasionally has the need for its use. Furthermore, the musculocutaneous flaps provide tissue from a nonirradiated field in most instances.

PHYSIOLOGIC PRINCIPLES. A musculocutaneous flap is a compound flap composed of skin and muscle that receives its blood supply from a dominant, vascular pedicle. The ideal musculocutaneous flap receives its blood supply from a large, named, longitudinally oriented, segmental artery coursing deep to the muscle mass along with a large vein and associated nerve. Arising from this segmental artery are perforating vessels that enter the muscle, supply it, and communicate with cutaneous vessels, which derive their blood supply from both the perforators and the segmental vessels. As noted previously, axial-pattern flaps are nourished by an anatomically recognized arteriovenous circulation following the long axis of the flap, and random pattern flaps are nourished by communications of vessels in the dermal–subdermal plexus. The basic physiologic principle determining the survival of all flaps is the concept of a self-contained vascular territory providing perfusion pressure to the distal edges of the flap. In other words, to ensure flap survival, a flap must have vascular channels

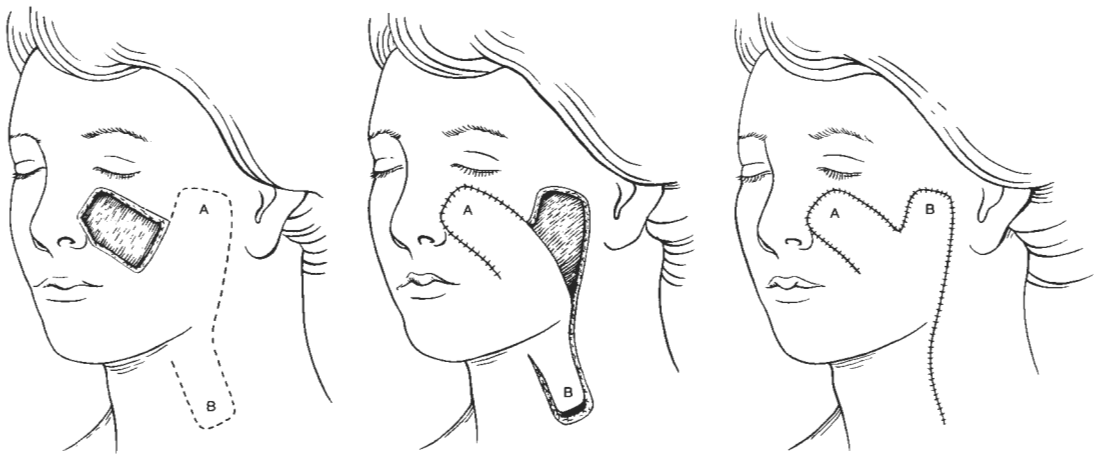

Figure 8-1. Bilobed flap. An example of a local transposition flap.

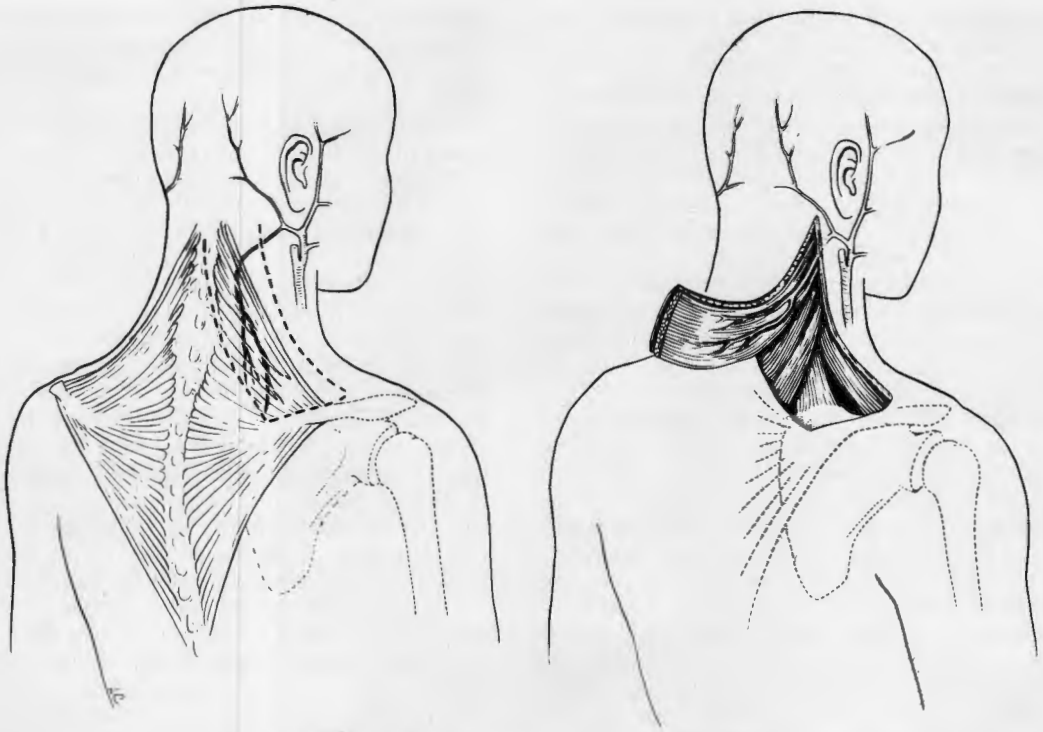

Figure 8-2. Nape of neck regional flap.

supplying and draining all of its portions. A flap containing an artery and vein along its long axis is limited only by the length of those vessels, and the maximum length of the random pattern flap is determined by the perfusion pressures in the dermal–subdermal plexus.

The human body contains many self-contained vascular territories capable of supporting musculocutaneous flaps. Five major pedicled musculocutaneous flaps are available to the surgeon working in reconstruction of the head and neck—the platysma, the sternocleidomastoid, the pectoralis major, the latissimus dorsi, and the trapezius. The platysma and sternocleidomastoid are supplied by smaller, less well-defined vessels, and flaps raised in these areas may survive but are more similar to random pattern flaps than to axial-pattern flaps. The pectoralis major, latissimus dorsi, and trapezius muscles contain a named arterial supply and closely applied overlying skin, allowing them to function as true axial-pattern musculocutaneous flaps. These flaps offer many advantages. They provide a one-stage procedure, and the donor site usually may be closed primarily. Long vascular pedicles allow the flaps to be transferred to the head and neck from distant, nonirradiated fields. Finally, the large segmental vessels ensure excellent perfusion pressures to the entire flap.

DELTOPECTORAL FLAP. Before the development of pedicled and free musculocutaneous flaps, the deltopectoral flap was the workhorse of the head and neck reconstructive surgeon. The deltopectoral flap has largely been replaced by more reliable and appropriately sized flaps. In the situation where cutaneous tissue alone is required, however, the deltopectoral flap is suitable. Disadvantages include the need for a second stage to divide the pedicle and the need for skin grafting of the donor site. It is an axial-pattern cutaneous flap based medially on the second, third, and fourth anterior perforating branches of the internal mammary arteries. The flap extends laterally over the deltoid muscle. Additional flap length may be obtained by elevating and delaying the flap before transfer (Fig. 8-3).

PLATYSMA MUSCULOCUTANEOUS FLAP. The platysma musculocutaneous flap has limited application for head and neck reconstructive surgery since more reliable flaps are available. The flap provides a one-stage procedure for closure of oral cavity defects, and the donor site may be closed primarily. It does have the advantage of providing a muscle–skin flap that relatively ap-

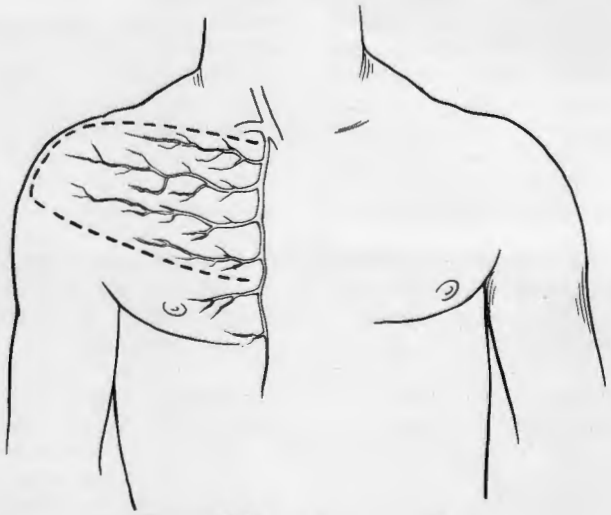

Figure 8-3. Deltopectoral flap.

proximates the thickness of normal oral mucosa and can easily be contoured to fit the defect.[6] About 75 cm^2 of epithelial coverage may be obtained, which comes to resemble oral mucosa; however, hair may grow on the flap, especially in men. No new surgical field is entered to obtain the flap. The major disadvantage is that preoperative irradiation of the neck may cause significant atrophy of the muscle and preclude an adequate vascular pedicle to support the skin paddle. Also, the flap is inadequate to provide heavy, thick coverage needed to cover a large area of exposed mandible. The platysma musculocutaneous flap has been used to resurface the floor of mouth, the tongue, the tonsillar fossa, and the buccal mucosa, with a greater than 90% success rate in 37 patients.[4]

The platysma muscle, lying in the superficial fascia of the neck, has its origin from the clavicle and the upper portion of the thorax, and its insertion over the border of the mandible superficial to the facial vessels. At the lateral angle of the mouth, the platysma blends with the facial muscles associated with the lower lip. The major blood supply to the platysma is the facial and transverse cervical arteries, and the innervation is provided by the cervical branch of the facial nerve. The surface defect in the oral cavity is measured, and a horizontal ellipse ranging from 5 × 10 cm to 7 × 14 cm is outlined on the neck skin overlying the platysma. To minimize pedicle tension, the ellipse is placed more anteriorly for anterior oral defects and more posteriorly for posterior defects. The pedicle length is estimated by measuring from the superior margin of the skin ellipse to the level of the mandible. The superior incision is made just through the skin, and the skin flap above the incision is elevated, leaving the subcutaneous fat attached to the platysma.

It is thought that a large part of the platysma blood supply is provided through a subdermal plexus, as in a random-pattern flap. Therefore, this is a critical maneuver in enhancing flap viability. Once the superior skin flap is elevated to the level of the mandible, the inferior incision is carried through the skin and platysma muscle. As with a neck dissection, the platysma–subcutaneous pedicle is broadly elevated from the underlying neck structures to the level of the mandible. The skin island of the platysma flap is reflected 270 degrees on itself and 90 degrees around the mandible so that the skin faces superiorly. The inferior edge of the skin ellipse is then nearer to the mandible, where it is sutured to the lateral resection margin, and the superior edge is nearer the tongue, where it forms one edge of the medial closure. The neck donor site is closed primarily over suction drains.

The complications associated with the use of this flap include partial or total cutaneous necrosis, separation of the closure, infection under the flap, and partial dehiscence of the neck donor site. The major reasons for failure are making the pedicle too thin and neglecting to leave the subcutaneous fat on the muscle pedicle.

STERNOCLEIDOMASTOID MUSCULOCUTANEOUS FLAP. The sternocleidomastoid flap has been described by Ariyan as an island flap capable of reconstructing defects in the oral cavity and neck and also as an aid in closing pharyngeal fistulas.[1] The skin island can be elevated from either an inferior base (the supraclavicular region) or a superior base (the mastoid area). A major drawback is the high rate of cutaneous necrosis. Also, an oncologic procedure could be compromised by raising the sternocleidomastoid flap; the use of this flap, therefore, is contraindicated by ipsilateral lymphatic disease. All things considered, the sternocleidomastoid musculocutaneous flap is not very powerful and is seldom the first choice for reconstruction of defects of the head and neck.

The sternocleidomastoid muscle has its origin in two heads from the medial third of the clavicle and the manubrium of the sternum; these two heads blend together just below the middle third of the neck. The muscle's insertion is into the lateral half of the superior occipital bone and the mastoid by means of an aponeurosis. Over the upper one third of the sternocleidomastoid, the skin directly overlies the muscle, but over the lower two thirds, the platysma is interposed between the skin and muscle. The blood supply of the sternocleidomastoid has three components. Inferiorly, the blood supply is from a branch of the thyrocervical trunk, whereas in the middle third, the muscle receives a branch from the superior thyroid artery. Superiorly, a branch of the occipital artery enters the muscle just below the mastoid region. The innervation of the sternocleidomastoid is provided by the 11th cranial nerve, which exits the skull through the jugular foramen.

A skin paddle is outlined as an island superiorly near the mastoid process or inferiorly over the lower neck and clavicular region. The muscle is then elevated after severing either its inferior attachments when an inferior skin paddle is chosen or its superior attachments when a superior island is being used. Although the flap may survive tenuously without its superior thyroid artery supply, the upper or lower two vascular pedicles should be preserved. The muscle and attached skin are then completely elevated from the deep structures of the neck (Fig. 8-4). The flap is then rotated into the defect medial to the mandible, and the donor site is closed primarily or with local flaps over suction drainage.

A significant incidence of partial cutaneous necrosis exists, although these flaps eventually will be covered with mucosa that grows in from surrounding epithelium. Speculation on the cause centers on the fact that the platysma lies between the sternocleidomastoid muscle

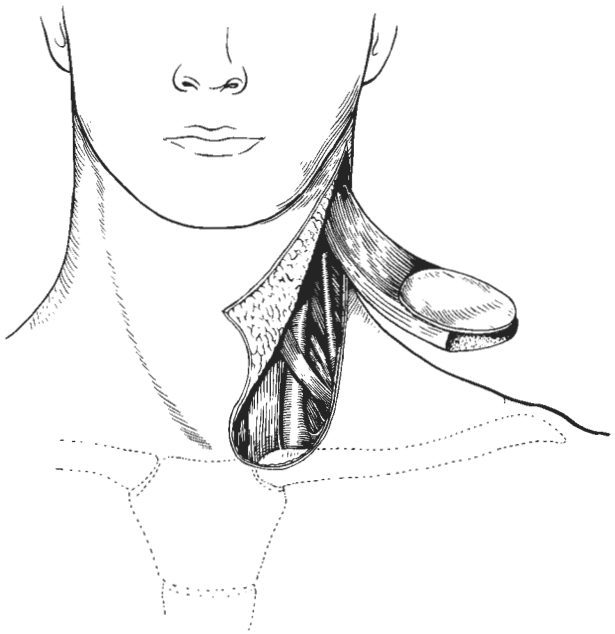

Figure 8-4. Sternocleidomastoid musculocutaneous flap.

and the skin. The overlying skin, therefore, may be functioning as nothing more than a full-thickness skin graft, and survival rates of intraoral full-thickness skin grafts are comparable.

PECTORALIS MAJOR MUSCULOCUTANEOUS FLAP. The pectoralis major musculocutaneous flap has become the most used one in head and neck surgery because of its great versatility and durability. The head and neck surgeon is relatively familiar with the anterior chest wall region, and the patient does not have to be repositioned during the procedure. This flap's durable pedicle and extra length make it a frequent choice for pedicled musculocutaneous reconstruction of large defects from the anterior mediastinum to the skull base. The viable cutaneous area can range up to 300 cm^2, and additional cutaneous coverage can be obtained by including randomly supplied chest skin. The large skin paddles can be designed in several fashions to reconstruct a variety of defects. Orocutaneous and pharyngocutaneous defects may be closed by placing a skin graft on the muscle side or by dividing the cutaneous portion and folding the muscle on itself. The flap may be tubed on itself to close esophageal and pharyngeal defects as well; the difficulty in tubing the flap and the high rate of distal stenosis, however, make other reconstructive techniques more appealing for this application. Because of its bulk, the pectoralis major flap functions well for soft tissue defects in mandibular reconstruction, coverage of great vessels, and filling of dead space in the field of resection. The pectoralis major flap donor site is rarely included in radiation therapy portals; the flap can therefore provide a fresh blood supply to a previously irradiated area. Potential disadvantages include its bulk, suboptimal color match, transfer of hair-bearing skin into the oral cavity, distortion of the breast after closure in women, and the restricted amount of contouring possible. Nevertheless, this is probably the most useful pedicled flap available in head and neck reconstructive surgery.

The pectoralis major is a large, fan-shaped muscle of the upper anterior chest wall arising from the medial half of the clavicle, the sternum, and the upper seven costal cartilages. Its insertion is into the crest of the greater tubercle of the humerus; the muscle acts as a medial rotator and adductor of the humerus. The nerve supply is composed of the lateral and medial pectoral nerves. The blood supply is most commonly reported to be the thoracoacromial artery; however, it has been demonstrated in cadaver dissections and angiographic studies that the lateral thoracic artery also plays a significant, if not equal, role in the blood supply. The pectoral branch of the thoracoacromial artery originates posterior to the pectoralis minor muscle, where it pierces the clavipectoral fascia medial to the pectoralis minor muscle tendon at about the midpoint of the clavicle. This segmental artery runs in the fascial envelope on the undersurface of the pectoralis major and does not give off branches to the pectoralis minor. The lateral thoracic artery originates from the axillary artery and pierces the clavipectoral fascia lateral to the pectoralis minor tendon. It then courses along the lateral border of the pectoralis major for 4 to 5 cm before running along its undersurface. A rich anastomosis exists between the lateral thoracic and thoracoacromial arteries, but the plane between the pectoralis major and minor muscles is avascular.

The required cutaneous paddle is outlined upon the chest wall medial to the nipple in men and medial to the breast in women. It is important to remember that the farther cephalad the defect is, the farther caudad the skin paddle must be placed. An incision is made down to the pectoralis fascia extending from the superolateral portion of the paddle to the deltopectoral groove, and the desired cutaneous paddle is incised. Place tacking sutures between the skin paddle and underlying muscle to prevent shearing of the skin from the muscle and from its underlying blood supply. If the need for a future deltopectoral flap is anticipated, then outline a deltopectoral flap rather than extending the superior incision into the deltopectoral groove. The deltopectoral flap then can be elevated and preserved for future use. Medial and lateral skin flaps are elevated using blunt and sharp dissection until the entire pectoralis major muscle is visualized. The cutaneous paddle and pectoralis major then are bluntly elevated off of the underlying pectoralis minor muscle. Next, the neurovascular bundle is visualized or palpated on the undersurface of the muscle, and the humeral attachment of the muscle is divided. If the vascular bundle is not visible, it can usually be found at a point one third of the way from the lateral head of the clavicle to the midline of the manubrium sternum. The incisions through the muscle may be carried out medially, laterally, and inferiorly at this point. The flap is freed from its sternal and costal attachments and elevated to its superior vascular hilum. While directly visualizing the pedicle, the muscular fibers medial to the pedicle may be divided to obtain more length. A tunnel then is created under the cervical skin, and the flap is passed through and positioned in the defect. Care should be exercised to make sure that the tunnel is adequate for the pedicle. The medial and lateral pectoral nerves may cross the vascular pedicle when the flap is rotated into the neck, compromising the blood supply. It may be necessary to identify and section these nerves. Excess tension should not exist after the flap is inset as traction on the pedicle can lead to vascular compromise. The chest wound is closed primarily in most cases, and the chest and neck wounds are appropriately drained (Fig. 8-5).

The complications associated with the use of this flap are the same as with most other flaps and include partial and total necrosis, suture line separations, fistulas, wound infection, recipient and donor site hematoma or seroma, donor site wound separation, and great vessel exposure with subsequent rupture. The most common cause of partial flap failure is poor perfusion in random portions of the flap, whereas the most common cause of total flap loss is venous outflow obstruction. In a series of 95 pectoralis major myocutaneous flaps in 86 patients, Ossoff and coworkers reported 33 complications, the most common of which were suture line dehiscence, fistulization, partial flap necrosis, and donor site hematoma or seroma. In view of the sheer bulk of the pectoralis major musculocutaneous flap, one should be especially alert for tumor recurrence under the flap and seek early detection and treatment.[11]

LATISSIMUS DORSI MUSCULOCUTANEOUS FLAP. This is a versatile flap with an arc of rotation that extends from the elbow to the sternum and up into the head and neck, and it can be rotated 180 degrees in either direction. The latissimus dorsi flap has been used to reconstruct defects of the cervicofacial skin, floor of mouth, the pharynx, and the cranial base. Up to 300 cm^2

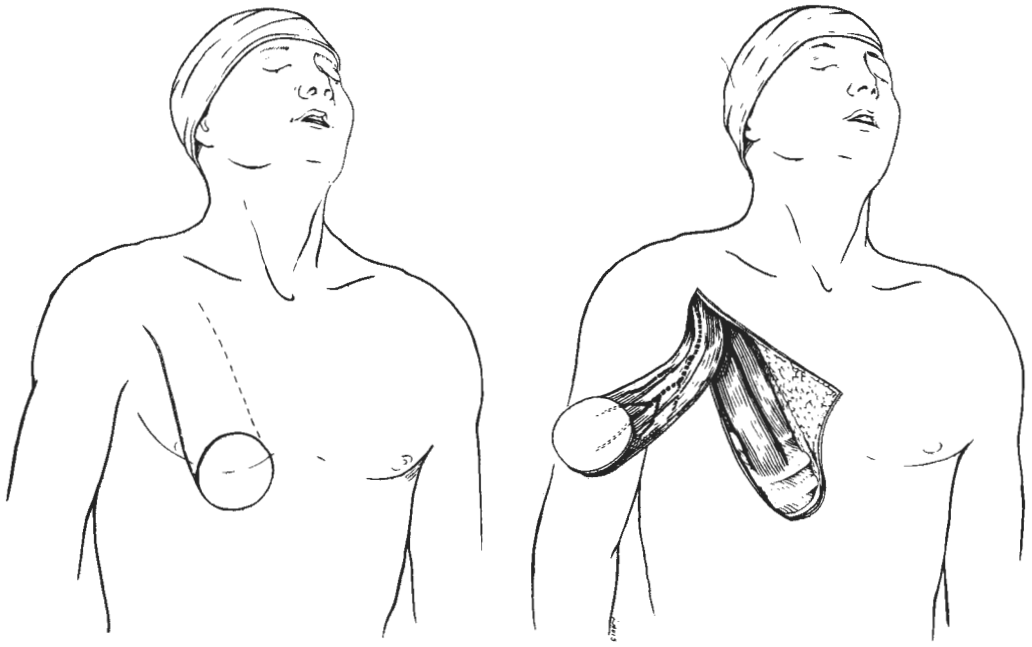

Figure 8-5. Pectoralis major musculocutaneous flap.

of cutaneous coverage may be obtained, and the flap may reach as high as the cranial vertex. As with the pectoralis major flap, the donor area is rarely included in radiation portals. Additional advantages are that the donor defect is minimal, the flap can carry a partial sensory innervation to the reconstructed area, and removal of the flap from the donor site has minimal to no effect on the position of the breast. This flap cannot be used if a previous axillary dissection has been performed. Also, if the 11th cranial nerve is sacrificed in a radical neck dissection, the resulting shoulder disability after latissimus dorsi elevation will be significant. The flap's significant problem is that the patient must be repositioned in a lateral decubitus position to harvest the flap. As with the pectoralis major flap, its sheer bulkiness may hide early tumor recurrence.

The latissimus dorsi is a flat, triangularly shaped muscle with its origin from the attachments of the thoracolumbar fascia to the spinous processes of the sacral vertebrae and the sixth through the twelfth thoracic vertebrae as well as from the iliac crest and the lower four ribs. The fibers run toward the axilla, spiraling 180 degrees to the insertion on the intertubercular groove of the humerus. The muscle acts by extending, medially rotating, and abducting the arm. Innervation is supplied by the thoracodorsal nerve, which is a branch from the posterior cord of the brachial plexus. A branch of the subscapular artery, the thoracodorsal artery, supplies the latissimus dorsi muscle. It passes inferiorly from the groove between the latissimus dorsi and serratus anterior muscles and gives off several branches to the chest wall before reaching the muscle. The artery and vein enter the undersurface of the muscle at a neurovascular hilus 2.5 cm behind its medial border. The subscapular–thoracodorsal pedicle is 8 to 12 cm long. Segmental perforating branches of the posterior intercostal artery may supply the posterior one third of the muscle. The artery and vein enter the muscle and then bifurcate into an upper transverse branch running across the superior border and a lateral vessel running longitudinally toward the iliac crest 2 cm from the lateral muscle border in about 86% of the patients, whereas the remainder do not have an upper transverse branch.

The patient first must be placed in a midlateral position with the arm elevated superiorly. The point of rotation for the latissimus dorsi is where the subscapular artery arises from the axillary artery just below the pectoral–humeral junction. The distance from the surgical defect then can be transposed along a line behind the anterior border of the muscle. The skin paddle is best placed between the 6th and 10th ribs. Next, the paddle is circumferentially incised down to the muscle, and an incision is carried up to the pectoral–humeral junction. Beginning inferiorly after tacking sutures are placed, the musculocutaneous paddle is elevated from below upward with direct visualization of the vascular pedicle. When adequate visualization of the pedicle has been achieved, the muscle can be dissected to the pectoral–humeral junction, where the muscle pedicle is transected just above the vascular pedicle's entrance into the muscle. Divide arterial and venous branches to the chest wall to provide extra flap rotation. A subcutaneous tunnel is created above or below the pectoralis major muscle, and the flap is passed through. Once again, no tension should be placed on the pedicle, and the tunnel should not be constrictive. Close the donor site primarily or with the aid of a split-thickness skin graft (Fig. 8-6).

The complications associated with this flap are similar to those of the other musculocutaneous flaps. The donor site complications, however, seem to overshadow any problems at the recipient site. Bulk remains a problem at the recipient site, as does partial cutaneous necrosis.

TRAPEZIUS MUSCULOCUTANEOUS FLAP. Multiple skin islands may be developed over the trapezius muscle; inferior and lateral paddles are most commonly used, however. Both the lower and lateral trapezius mus-

culocutaneous flaps survive well, are thin and hairless, and may be used to reconstruct defects in the pharynx, cheek, floor of mouth, and neck skin. Compared with the pectoralis major flap, the trapezius flap is technically more difficult, is less bulky, and provides a less noticeable donor site deformity. The major disadvantage of the lower flap is that the patient must be repositioned in the lateral decubitus position during surgery. Also, the transverse cervical vein may be short sometimes and will limit the arc of rotation, particularly for the lateral trapezius flap. The lower trapezius flap is more advantageous than the lateral flap because the skin island may be placed more distally from the rotation point, allowing for its use in a more distant position.

The trapezius muscle is a flat, triangular muscle of the upper back, neck, and shoulder with its origin in the external occipital protuberance, the ligamentum nuchae, and the spinous processes of cervical and all thoracic vertebrae. Its insertion is on the posterior border of the lateral third of the clavicle, the medial margin of the acromion, and the posterosuperior spine of the scapula. Innervation is supplied by the 11th cranial nerve. The dominant blood supply is provided by the superficial branch of the transverse cervical artery.

Several branches of the occipital artery supply a portion of the upper trapezius. The transverse cervical artery arises from the first part of the subclavian artery in about 80% of cadaver dissections, usually off the thyrocervical trunk. From this origin, the artery passes behind the sternocleidomastoid and omohyoid muscles to the anterior border of the levator scapulae where the artery divides into superficial and deep branches. The superficial branch crosses the levator scapulae along with the accessory nerve and passes deep to the anterior border of the trapezius 2 to 5 cm above the clavicle. It continues under fascia of the muscle to supply the middle and lower portions of the trapezius muscle. At this point, it continues as an ascending and a descending branch.

Considerable variability exists in the origin of the transverse cervical artery, and in about 20% of cases, it arises directly from the third portion of the subclavian artery. In this case, the artery may run deep to or through the brachial plexus, severely limiting the rotation of the flap. The multiple transverse cervical veins run superficial to the omohyoid muscle and enter the external jugular vein most frequently low in the neck, just above the clavicle, at the site of entrance of the external jugular vein into the internal jugular vein. This is highly variable, and it may enter the external jugular vein much higher or directly enter the internal jugular vein.

The patient is placed in the supine position for the lateral trapezius musculocutaneous flap, with a shoulder roll placed to provide access to the upper and lateral portion of the shoulder. The acromioclavicular joint is identified with the patient sitting upright before the procedure. During the ipsilateral neck dissection, the transverse cervical artery and vein are identified and preserved. A skin paddle is outlined about 6 to 8 cm lateral to the acromioclavicular angle, and the skin margins are elevated off the deltoid muscle until the acromioclavicular joint is identified. The trapezius is identified and freed from the clavicular and acromial insertions. The trapezius is elevated along with the skin paddle and is incised medially to the previously identified transverse cervical artery and vein. The skin muscle island is then free on a vascular pedicle and is ready for rotation into the defect.

For the lower trapezius musculocutaneous flap, the patient is placed in the lateral decubitus position with the upper arm internally rotated and abducted to rotate the scapula into a lateral position. An appropriate skin island is positioned over the middle to lower back with the distance from the subclavian determined by the length needed to reach the defect. The island then is incised down to the trapezius muscle and through it inferiorly. A single incision is made superiorly from the island to the anterior border of the trapezius, and the skin is

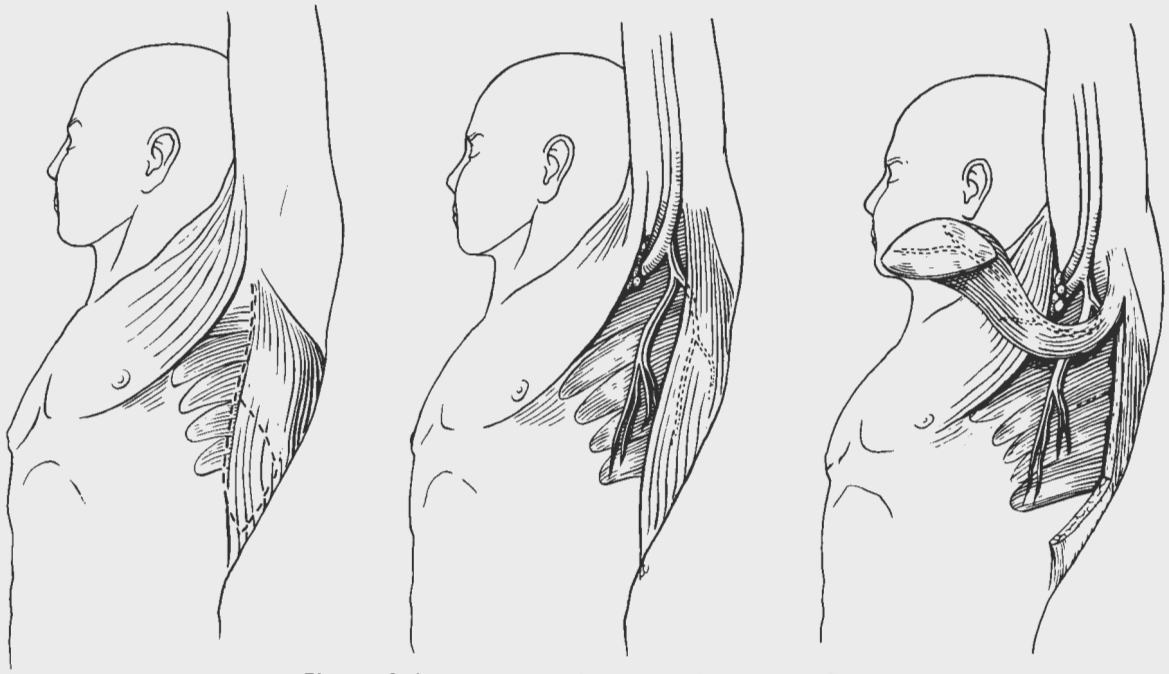

Figure 8-6. Latissimus dorsi musculocutaneous flap.

elevated medially and laterally until the lateral edge of the muscle is identified. Using blunt dissection, the trapezius is freed from the underlying rhomboideus muscle. The trapezius muscle next is separated from it insertions to the vertebrae and the scapula, allowing elevation of the skin–muscle flap and identification of the descending branch of the transverse cervical artery on the undersurface of the muscle within the fascia. The vascular pedicle is mobilized to the medial margins of the neck, and the flap is brought into the defect through a subcutaneous tunnel. The 11th cranial nerve may be preserved if the flap can rotate into the defect; otherwise, it is sacrificed. After the flap is sutured into place over suction drainage, the donor site is closed primarily, again over suction drains.

Partial necrosis of the flap is the major complication encountered, along with shoulder disability similar to that associated with classic radical neck dissection. As with other musculocutaneous flaps, dehiscence and wound infection are significant problems.

TRAPEZIUS OSSEOMUSCULOCUTANEOUS FLAP. This flap gained popularity as a one-stage reconstruction of mandibular resection defects. Better alternatives are available, specifically, the microvascular free tissue transfers, which are able to deliver larger, more appropriately shaped bony segments. Operative technique remains the same as with the lower trapezius musculocutaneous flap except that an appropriate length of the spine of the scapula is elevated up with the skin–muscle flap. This flap is possible because the spine of the scapula, being a flat bone, receives its major blood supply from the muscle rather than from an endosteal blood supply. The scapular spine is affixed to the remaining mandible with osseous wiring or plating and optionally stabilized with external fixation. The complications are similar to those of the musculocutaneous flap with the addition of necrosis or nonunion of the bone segment.

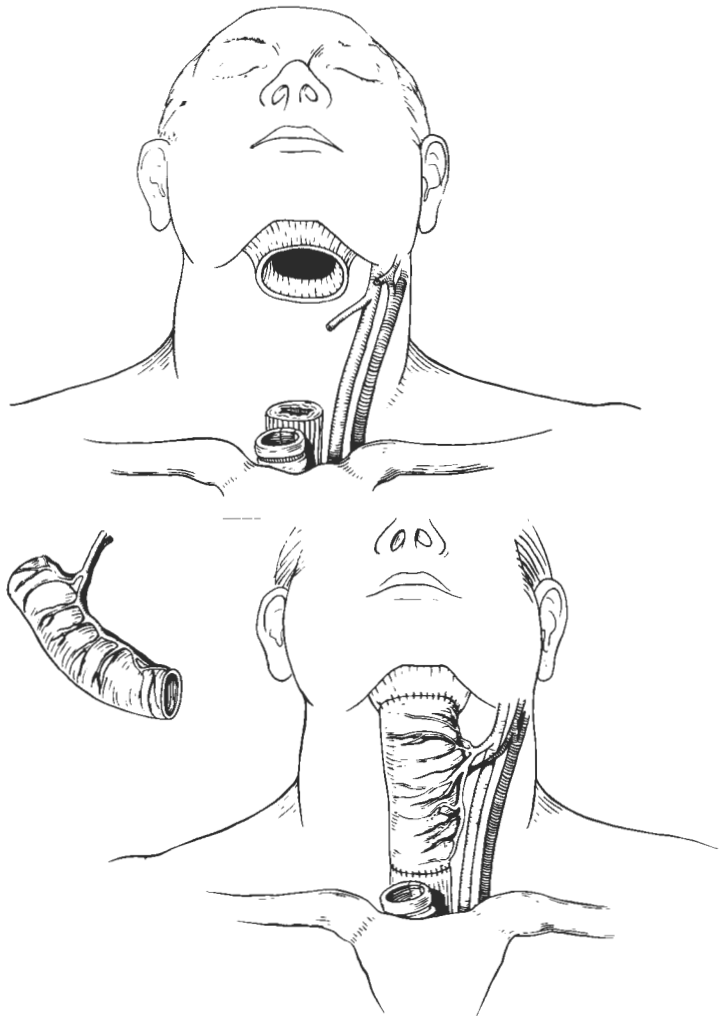

Figure 8-7. Jejunal interposition free flap for hypopharyngeal defect.

Free Tissue Transfer

Microvascular techniques have allowed the transfer of free cutaneous, alimentary, or compound flaps for difficult reconstructive situations involving the mandible, pharynx, oral cavity, and soft tissues of the head and neck. The use of microvascular surgical technique is more time consuming, possibly increasing complication rates, and requires extensive training not available to all surgeons. Most defects of the head and neck may be suitably reconstructed with pedicled regional or distal flaps. When primary mandibular reconstruction is necessary, however, or when thin, pliable, one-stage cutaneous flaps are desired, free tissue transfer excels. The island nature of the flaps allows for easier positioning in the defect, and the lack of a fixed pedicle prevents future tethering. Additionally, reconstruction of the hypopharynx after total laryngopharyngectomy with esophageal preservation is readily accomplished with a free jejunal interposition[3,7] (Fig. 8-7). The indications for the use of jejunal free flaps are more extensively discussed in Chapter 21.

Virtually any tissue with a closed arterial–venous circulation with vessels greater than 0.8 mm in external diameter may be transferred as a free flap. Early microvascular transfer of tissue was largely limited to cutaneous flaps after the first successful transfer of a free groin flap by Daniel and Taylor in 1973.[5] Since then, the transfer of osseous, musculocutaneous, osteomusculocutaneous, and osteocutaneous free flaps has been accomplished.

Patient Selection

Although free flaps may be transferred on virtually any patient, several factors may potentially adversely affect the outcome. Advanced age is frequently associated with atherosclerosis and diabetes mellitus, which may result in thickening of the walls of small arteries and increased vascular fragility. Obesity may make the dissection of the vascular pedicle itself more difficult and be associated with an overly thick cutaneous flap. Certain systemic illnesses such as coagulopathy, collagen vascular disease, and polycythemia may preclude the use of microvascular techniques.

Previous radiation therapy to the donor or recipient site may present disadvantages. Early radiation changes in the vessels of the size used for anastomoses include edema and necrosis of the endothelium and subsequent thrombosis. Later effects include fibrosis and endothelial proliferation, which produces luminal narrowing. However, Baker and colleagues examined the effects of preop-

erative irradiation on microvascular anastomoses performed 4 weeks later. Radiation effects were readily apparent in the vessels, yet the patency rate was not affected.[2]

Surgical Technique

The use of meticulous surgical technique and preoperative planning is extremely important in obtaining a successful outcome with free tissue transfer. While the ablative team removes the tumor, the reconstructive team begins the flap harvesting. Typical recipient vessels prepared include the superficial temporal, facial, superior thyroid, lingual, and superficial cervical arteries; and the superficial temporal, facial, external jugular, and internal jugular veins. The recipient artery is observed for vigorous pulsatile blood flow when transected. The particular flap to be transferred is outlined, and the vascular pedicle is identified. Contributory vessels are ligated to provide maximal pedicle length. The vascular pedicle is transected when the recipient site is completely prepared. Careful anastomosis of the donor and recipient vessels then is performed, and the anastomotic site is observed for hemostasis and patency. Next the flap is inset into the defect.

Complications

Microvascular free tissue transfer has complications similar to those of pedicled transfers but additionally carries risks unique to the technique. As with any closure of oral or pharyngeal tissue, fistulas may occur. Donor site complications such as seroma or infection may be problematic. Partial flap necrosis is more common than total flap necrosis, and this is due more often to extending the flap beyond the territory of the vascular pedicle than to a faulty anastomosis. Arterial thrombosis usually occurs in the first 24 to 72 hours and is heralded by a decrease in the flap temperature, loss of tissue turgor, and loss of capillary refill. Venous thrombosis is more common but may occur later. This is associated with swelling of the flap and a change in color. Prompt reexploration for either of these problems may result in salvage of the flap. The salvage rate is highly associated with the speed of recognition of an anastomotic complication. Monitoring techniques such as laser Doppler cutaneous blood flow measurement and constant flap temperature observation are useful for detecting early changes. As previously mentioned, a variety of cutaneous and compound flaps are available for free transfer. Increased understanding of vascular territories has led to a significant increase in the number of such flaps used. Some of the more common free flaps employed for reconstruction of defects of the head and neck are reviewed. The choice of flap depends largely on the tissue to be replaced. Other considerations include donor site morbidity, technical difficulty of flap harvesting, and patient positioning requirements.

Cutaneous

GROIN. The groin flap was the original cutaneous free flap to be transferred. The superficial circumflex iliac artery, usually a direct branch of the femoral artery, is the dominant vascular supply. Large areas of skin may be harvested for resurfacing of cutaneous or oropharyngeal defects. The donor site usually is closed primarily with a resultant cosmetically acceptable scar. The groin flap has two distinct disadvantages: the vascular stalk is limited, and the vascular anatomy may be variable. Also, the flap may be bulky in obese patients. The short vascular pedicle and bulkiness have limited its clinical use in the head and neck.

DORSALIS PEDIS. The dorsalis pedis flap is based on the dorsalis pedis artery, which is a terminal branch of the anterior tibial artery. It is thin, easily harvested, and has a long vascular pedicle associated with a sensory nerve. However, the vascular supply is variable and also may be affected by atherosclerosis in older patients. A split-thickness skin graft is required to close the donor site, which may cause significant morbidity.

DELTOPECTORAL. The free deltopectoral flap is based on the second perforator of the internal mammary artery and is relatively easy to harvest. Large areas of thin skin with a good color match for the face can be obtained. It is not necessary to extend the flap laterally to a large extent since the pedicle will not remain attached. This obviates the need for using distal random-pattern tissue.

The availability of other flaps with more easily closed donor sites has limited the use of this flap. In addition, the close proximity to the head and neck limits the ability to simultaneously harvest the flap and excise the tumor. Microvascular anastomosis is limited by the short vascular pedicle.

RADIAL FOREARM. This forearm flap is supplied by the radial artery with venous drainage through the cephalic and basilic veins. Positioning of the patient to harvest the flap is straightforward. The flap itself consists of thin, pliable skin with a long pedicle of large-diameter vessels. Viability of the hand after sacrifice of the radial artery is assured preoperatively with the Allen test. The thin nature of the flap makes it suitable for intraoral reconstruction. A portion of the radius may be included for bony reconstructions as well. Skin graft failure at the donor site is the most significant complication.

The superficial branch of the radial nerve may be transferred with the flap to provide a vascularized nerve graft for repair of motor nerves, or the antebrachial nerves may be included to anastomose to a sensory nerve, potentially creating a sensate flap.[14]

SCAPULAR. The scapular cutaneous flap provides a long pedicle and large-diameter vessels. Its blood supply is a branch of the circumflex scapular artery, which emerges from the triangular space bounded by the teres minor, teres major, and long head of the triceps. The donor site may be closed primarily in most cases. The thickness of the tissue is intermediate between the thin radial forearm flap and the bulky latissimus dorsi musculocutaneous flap.

Compound

GROIN. The free osteocutaneous groin flap has been widely used in the reconstruction of mandibular defects. The blood supply is the deep circumflex iliac artery, which arises off of the external iliac artery. A large segment of bone may be harvested for mandibular defects in association with cutaneous tissue for intraoral resurfacing. An extensive, time-consuming dissection is required to obtain the flap. Significant donor site deformities in-

clude hematoma, prolonged pain, and hypesthesia. A careful closure is required to prevent postoperative hernia formation.

LATISSIMUS. The latissimus dorsi muscle is transferred alone or with skin by means of microvascular technique when a pedicled flap is undesirable. The vascular anatomy is the same as with the pedicled flap, and the vascular pedicle is long. Donor site morbidity is reasonable; the flap is bulky, however.

RECTUS ABDOMINIS. The rectus abdominis is transferred as a muscle flap or as a musculocutaneous flap based on the inferior epigastric artery. The muscle flap is especially useful for closing large anterior cranial base defects after craniofacial resection. The donor site may be closed primarily without significant morbidity.

SCAPULAR. The scapular cutaneous flap may be harvested as an osteocutaneous flap as well by including the lateral border of the scapula. The thin cutaneous tissue and revascularized bone are most useful for primary reconstruction of mandibular continuity defects.

OMENTAL OR GASTROOMENTAL. The gastroomental flap has been used as a free flap for resurfacing of oral cavity and oropharyngeal defects. A flap of stomach with its attached omentum is harvested from the greater curvature and based on the gastroepiploic artery and vein. It provides a non–hair-bearing, mucus-secreting lining for the oral cavity. The need for an intraabdominal procedure for harvesting adds to the postoperative morbidity.

The omentum alone may be transferred as a free flap and is especially useful for the repair of large scalp and dural defects, facial defects, or in the treatment and repair of osteoradionecrosis. The prime advantage of this flap is its rich vascularity and excellent pliability.

INTERNAL OBLIQUE–ILIAC CREST. Although numerous methods for restoring mandibular continuity after mandibulectomy exist, few are successful in restoring functional mastication. The internal oblique–iliac crest flap may be harvested as a osseomusculocutaneous flap based on branches of the deep circumflex iliac artery and used for primary reconstruction of mandibular defects. Furthermore, osseointegrated implants may be placed directly into the transferred revascularized iliac crest bone to allow the eventual use of a denture. Complications include partial or total flap loss, need for anastomotic revision, donor site pain, and death.[13]

GRAFTS

A graft may consist of any transferred tissue that must establish a new blood supply at the recipient site. The ready availability and immune compatibility of autografts make them a popular choice for reconstruction. Additionally, the operative time associated with such grafts is typically much less than with pedicled or revascularized tissue transfers.

Skin

All skin grafts must obtain their new vascularity from the recipient bed. It follows, therefore, that the thicker the graft, the more difficult it is to establish sufficient capillary ingrowth. Although all skin grafts contract to some degree, thinner grafts contract more significantly.

Skin grafts may be further classified according to the levels of skin transferred. Full-thickness skin grafts include the entire epidermis and dermis. Therefore, the donor site must be closed primarily, limiting the amount of tissue available for transfer. The most common donor sites in the head and neck are the supraclavicular fossa and the postauricular crease. These areas supply sufficient tissue for transfer, yet allow primary closure with camouflage of the scar. Full-thickness skin grafts are primarily used to resurface skin defects of the face or neck after resection of a squamous or basal cell carcinoma. Local flaps provide a better color match and skin thickness, however.

If some portion of the dermis is left at the donor site, then the graft is referred to as a split-thickness graft. In this case, the epithelium will regrow to cover the donor defect adequately. The most common donor sites are the thigh and buttock. Split-thickness skin grafts are used to provide epithelial coverage in any area when primary closure is impossible. Better alternatives exist for facial skin reconstruction, as mentioned previously, because color and tissue thickness match are poor in this instance. Split-thickness skin grafts are used most often to resurface oral cavity or maxillectomy defects. Split-thickness skin graft closure after the resection of oral cavity cancers, compared with the use of musculocutaneous flaps, allows better postoperative function with less perioperative morbidity.[9,12] Therefore, split-thickness skin grafts are recommended as the reconstructive option of choice for moderate defects of the oral cavity, and musculocutaneous flaps are reserved for massive defects.

Finally, the epidermis may be elevated to allow the harvesting of a dermal graft. Dermal grafts may be obtained from the same sites as split-thickness skin grafts with less donor site pain because the epidermis is replaced to allow for primary healing. Dermal sites may be used to resurface oral cavity defects as well. There may be less contracture with dermal grafts compared with split-thickness skin grafts because of the extra thickness. Dermal grafts also may be employed to provide coverage of the carotid artery after radical neck dissection. Theoretically, this additional layer of tissue reduces the risk of carotid blowout, especially in the presence of a pharyngocutaneous fistula. This may not be significant clinically, however, as Hillerman and Kennedy retrospectively reviewed 194 radical neck dissections and did not identify any difference in the rate of carotid rupture with or without dermal graft coverage.[8]

Mucous membrane grafts are an excellent choice for resurfacing oral cavity or conjunctival defects. Their use is somewhat limited by the small amount of tissue available for transfer and by the donor site morbidity.

The major complications of skin grafts are failure of the graft and contracture. Immobilization and compression of the skin graft prevent shearing of the neovascular supply and retard hematoma formation, thereby enhancing the graft's revascularization. This may be achieved with a bolster (Fig. 8-8) or with the use of so-called pie crusting and tacking sutures. All grafts contract to some degree, which varies with the thickness of the graft, as mentioned previously. Beginning with excess graft material loosely laid into the defect may retard significant contracture.

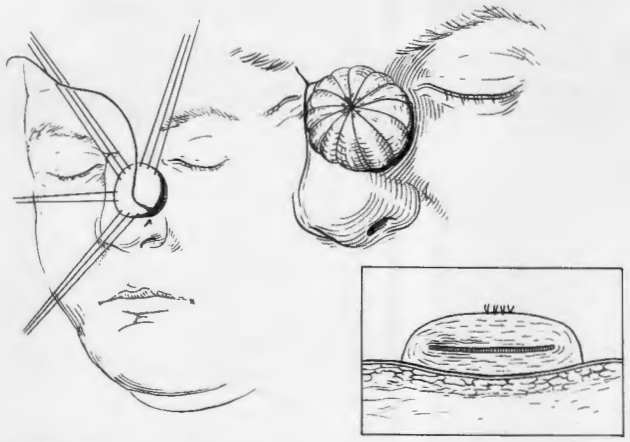

Figure 8-8. Bolstering technique for skin graft to the nose.

Bone

With the advent of revascularized bony free flaps, the indication for the use of nonvascularized bone grafts for head and neck reconstruction is fairly limited. However, mandibular reconstruction at a second stage may be accomplished by the use of iliac crest cancellous bone in a cadaveric mandibular cortical tray. The use of cadaveric bone avoids the problem of extrusion associated with metallic or synthetic trays. The most common complication after the harvest of iliac crest bone is donor site pain. Infection and graft failure may occur at the reconstructed site.

Cartilage

The indication for using a cartilage graft in operations for head and neck cancer is in the reconstruction of nasal alar defects. In this situation, a composite graft of skin and cartilage is harvested from the pinna and inset into the alar defect (Fig. 8-9). Since the graft depends on blood supply from the recipient site, the size of the graft is limited. The most common complication is necrosis of the graft. The marked tendency for cartilage to resorb effectively limits its use as a graft in most other situations. Small amounts of cartilage may be required to reconstitute the tarsal plate after resection of an eyelid cancer.

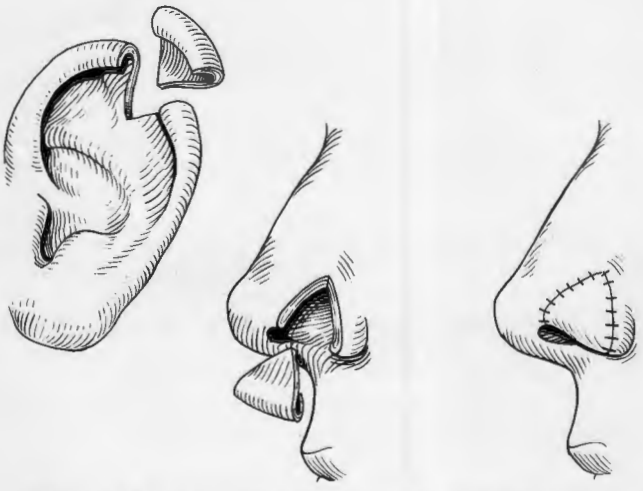

Figure 8-9. Composite auricular graft for alar defect.

Nerve

After total parotidectomy with facial nerve sacrifice or partial temporal bone resections, the facial nerve is most effectively reconstructed with an immediate primary cable nerve graft. The nerve graft serves as a conduit for regeneration of the peripheral nerve axons. The sural nerve and greater auricular nerve are the most common donor nerves because of the limited functional deficit, similarity in size to the facial nerve, and accessibility.

Fibrous growth into the anastomotic sites is the most common cause of failure. The best management of this problem lies in prevention through meticulous surgical detail. After the nerve ends are sharply freshened, the epineurium is trimmed back from the edges. The perineurium is then reapproximated without tension using fine suture material. Even with the most careful anastomosis, attempts to move a portion of the face cause the entire face to move, as a result of misdirected regrowth of the axonal fibers. Primary grafting is almost always preferable to secondary grafting or hypoglossal–facial nerve anastomosis. Even when postoperative radiation therapy is planned, excellent return of facial tone still may be expected.[10]

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9

MAXILLOFACIAL PROSTHETICS

GLENN E. TURNER

The importance of maxillofacial prosthetics in the treatment of cancer of the head and neck is intimately related to the quality of patients' lives. Quality of life means different things to different people. The varying degree of functional and cosmetic success of prostheses is illustrated by the histories of two famous people, President Grover Cleveland and Dr. Sigmund Freud (see Chap. 1).[2] Maxillofacial prosthetics developed from a dental background because making accurate impressions, sculpting in wax or other plastic materials, and coloring of artificial materials to match living tissues are basic skills that have been developed by dentists in general, and prosthodontists in particular. The role of maxillofacial prosthetics occurs mainly during the restorative and rehabilitative phases, but it also occurs in conjunction with and immediately after cancer therapy.

MAXILLOFACIAL PROSTHESES USED DURING RADIATION THERAPY

Prosthodontic stents provide significant benefit to the radiation therapist by enhancing the delivery of radiation therapy to local areas. Stents are used to protect or displace vital structures, to locate diseased tissues in repeatable positions, and to carry radioactive material to the tumor site.[1]

A device used to position oral structures and to fill the air space formed by the palatal vault is shown in Figure 9-1. The carcinoma was located on the palatal gingiva near the maxillary left first molar. The radiation therapist stated that the stent should completely and uniformly fill the palatal vault with a specific material so that the tumor dose could be calculated more accurately. In addition, the device should be designed to push the mandible and the dorsum of the tongue away from the maxilla, so that the mandibular structures would be out of the field of treatment. The stent was made of heat-cured acrylic resin. It was constructed by making an intraoral impression with thermoplastic material (modeling plastic); a mold made from this pattern then was used to process the acrylic stent. The patient was able to place the stent in one piece and to maintain the relationship of the mandible to the maxilla during repeated radiation treatments.

Devices known as *radiation carriers* are used to position radioactive sources. For example, it was decided to treat a patient with a radiation carrier for tumor recurrence in the nasopharynx because he had been treated previously with a maximum dose of external-beam radiation. The location of the tumor required the use of six radiation sources with an angle being made between the two superior sources and the four inferior sources; the angle produced an area of increased radiation dose at the level of the tumor. An acrylic resin block was constructed from an impression of the nasopharynx (Fig. 9-2). This impression was made in the operating room using modeling-plastic impression compound, with the patient under general anesthesia. The right side of the radiation carrier shown in Figure 9-2 touched the posterior wall of the nasopharynx, and the superior portion filled the posterior aspect of the nasal cavity. The radiation sources were placed by cutting two parallel channels at an equal distance from the posterior wall of the carrier. Polyethylene tubing of the same diameter as the radiation sources was placed in the channels and secured with autopolymerizing acrylic resin. Two holes were made in the superior portion so that gauze strips could be tied to the carrier. Radiation sources were loaded into the carrier. With the patient awake, the carrier was placed into the nasopharynx by using two rubber tubes placed into the nostrils and pushed posteriorly until they appeared below the soft palate. The gauze strips were tied to the rubber tubes and the carrier was pulled into place. Roentgenograms were made to verify the position of the radiation sources.

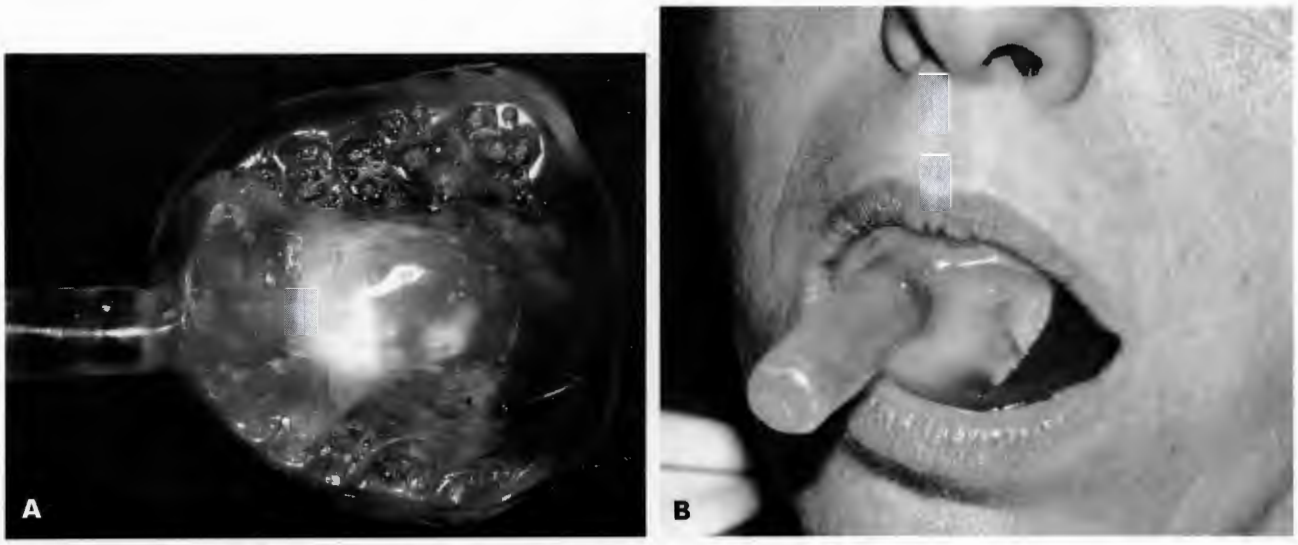

Figure 9-1. (*A*) Stent used to protect and displace vital structures during radiation treatments. (*B*) Stent in place.

Figure 9-2. (*A*) Acrylic mold of nasopharynx for radiation carrier. (*B*) Lateral roentgenogram shows implant in patient.

PROSTHETIC RESTORATION AFTER MAXILLECTOMY

Maxillectomy—including removal of the hard palate, partial removal of the soft palate, and/or orbital exenteration—is the most common operation for cancer that creates an intraoral defect. Patients with this defect have an excellent prognosis for rehabilitation. The materials and techniques that are used result in a durable, functionally satisfying, and aesthetically pleasing prosthesis, which camouflages the presence of a surgical defect.

The initial prosthesis should be placed at the time of the operation. Patients need an intraoral prosthesis to continue swallowing and speaking. The prosthesis used in this situation is termed the *surgical obturator*. The surgical obturator is replaced by the *interim obturator*, and when healing is complete, the *definitive obturator* is constructed.

The main objectives of the surgical prosthesis are to seal off the maxillary defect created between the oral and nasal cavities, and to hold the packing close to the split-thickness skin graft that lines the inner aspect of the cheek. Patients are able to speak and swallow immediately after surgery, and the nasogastric tube can be removed 1 to 2 days postoperatively. The prosthesis has a psychological effect that makes the postoperative course easier: patients are aware that rehabilitation has begun.[3] The quality of the result depends on location and size of the defect, prior radiation therapy, quality of the remaining tissue, surgical complications, and whether patients are dentulous.

The definitive prosthesis is made when healing is complete and remodeling of the defect has stabilized, usually 4 to 6 months after surgery, radiation therapy, or both. Dental preparation of the mouth and teeth should be completed or else be planned as an integral part of the fitting of the definitive prosthesis. This prosthesis should restore optimum function and provide a cosmetic result like that of the interim prosthesis but on a long-term basis.

Planning of Surgical Extent and Resulting Defect

Close cooperation between the surgeon and the prosthodontist is necessary for a good result. Planning includes a thorough dental evaluation to determine which teeth and structures will be retained during surgery.

Frequently, the surgical procedure can be slightly modified, without compromising the surgical result, so as to be helpful to prosthodontists and patients. As a general rule, the more hard palate and premaxilla that is retained, the better the prosthetic result. This applies in both dentulous and edentulous patients. The retention of certain key teeth, such as a molar posteriorly and the canine anteriorly, can greatly aid rehabilitation, if this can be done without compromising tumor resection. The entire prosthesis should be planned before the surgical resection, with particular emphasis on the mode of support that the remaining structures will provide for the prosthesis, the amount of stability available for lateral bracing, the amount and mode of gaining retention to resist movement of the prosthesis from the basal seat, and the cosmetic and functional results. The surgeon outlines the incision on a diagnostic cast of the maxilla, from which the extent of the surgical prosthesis is determined (Fig. 9-3). The initial prosthesis is attached to patients by sutures, wires, or a palatal screw, depending on size and extent of the defect.

Incision and Surgical Modifications

The bony incision is made along the hard palate (Fig. 9-4). It is advantageous to place the mucosal incision 4 to 5 mm lateral to the bony incision to enable the mucosal tissue from the hard palate to be used as a *rollover flap* at the midline of the defect. Palatal mucosa is more resistant to abrasion than is the nonkeratinized epithelium of the nose. Having a straight, smooth, bony margin is essential to reduce irritation of the mucosa by the prosthesis. If a maxillary torus is present, remove it with the initial bony incision.

Lining the reflected cheek flap with a split-thickness skin graft also provides benefits to rehabilitation. The skin graft is more resistant to irritation caused by the prosthesis, and it increases the flexibility of the cheek flap. In addition, the scar band that forms at the junction of the skin graft and the mucosa tends to contract, leaving a superolateral undercut, or ledge, that can be used in prosthesis construction to aid in retention and lateral stability.

Retention of the prosthesis in an edentulous patient is a greater challenge. This usually can be managed by a three-point undercut engagement: (1) posteriorly over the cut surface of the soft palate, (2) laterally by the undercut created by the scar band, and (3) anteriorly by the floor of the nose (Fig. 9-5). This engagement can be buttressed or braced against the medial wall of the defect, which should be covered by *palatal mucosa* overlying the cut margin of the resected hard palate. The three-point engagement is aided by the retention of as much hard palate and alveolar ridge as possible.

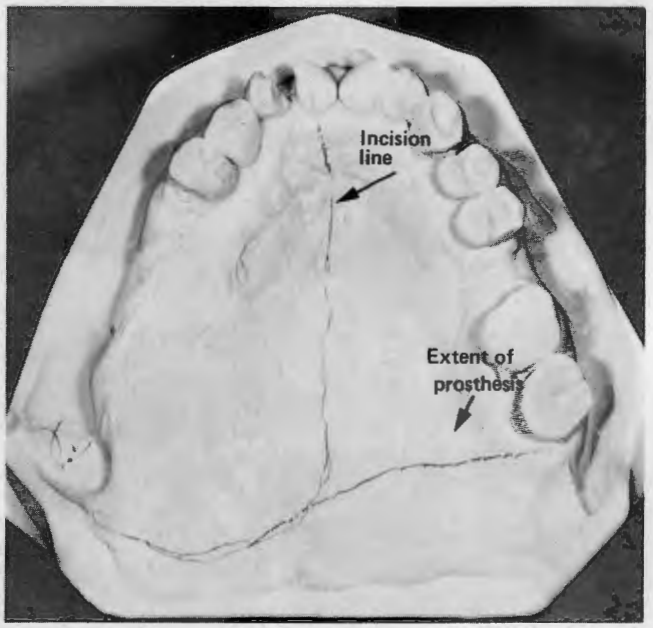

Figure 9-3. The incision is outlined by the surgeon on a diagnostic cast of the maxilla.

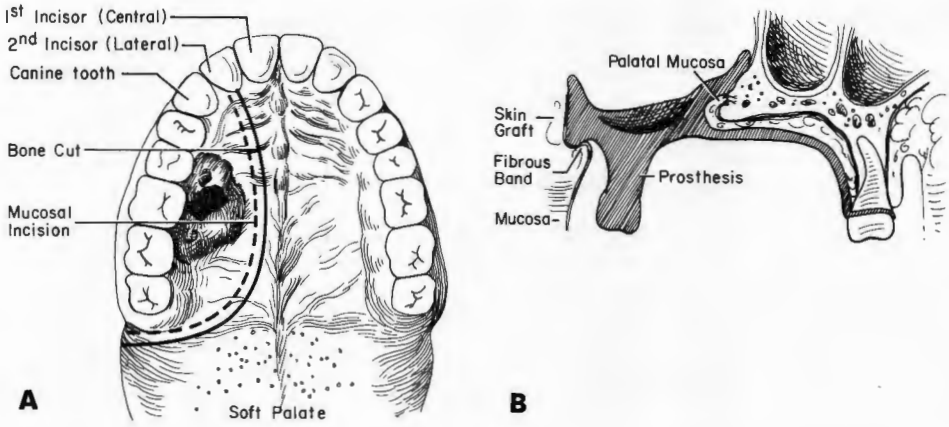

Figure 9-4. (*A*) The mucosal incision is placed 4 to 5 mm lateral to the bony incision. The bony incision is placed through the socket of the extracted tooth next to the last remaining tooth. (*B*) The prosthesis should be made so as to engage the undercut on the palatal shelf and the soft tissue of the buccal mucosa above the fibrous scar band.

In dentulous patients, retention of the prostheses can be attained by using the remaining teeth. However, these teeth should not be compromised by the surgical procedure. The bony cut through the alveolar ridge should be made as far away from the remaining teeth as possible (see Fig. 9-4*A*). This enhances the bony support important to the retention of a prosthesis. Retaining the canine tooth rather than the central or lateral incisor affords more stability for the prosthesis. If this is not possible, extract the lateral incisor and make the bony cut through the resulting socket. This allows 4 to 5 mm of bone next to the central incisor, and improves the clinical prognosis of that tooth.

In situations in which there is a large resection posteriorly and laterally involving the soft palate, retaining even a small band of soft palate tissue greatly enhances the posterior retention of the prosthesis (Fig. 9-6).

Special Problems

Problems and difficulties encountered by the dentist in restoring the hard and soft palate are due to complications of surgery (such as trismus), lack of anatomic base, or tissue sensitivity.

The most common problem for patients is leakage of air, liquids, and solids around the prosthesis into the nose. Leakage results from a faulty obturator seal between the oral and nasal cavities. The seal never is complete, since tissues surrounding the obturator move during function and create voids in the seal. Most of the leakage occurs because of the downward movement of the prosthesis posteriorly. Liquids then are forced up posteriorly when swallowing, as the tongue closes against the palate in a front-to-back direction. This problem, embarrassing to patients, usually can be controlled by making changes in the contours of the obturator. In addition, patients should be instructed to swallow with their heads tilted horizontally or slightly upward. Gravity then forces the fluids downward and away from the nasal cavity, and leakage is minimized.

The anterior maxillectomy presents a special problem from a restorative point of view. The missing anterior maxilla is replaced by a cantilever prosthesis with no anterior retention or support. Retention usually is obtained by engaging the nasal surface of the residual hard palate and by making an extension into the external nares from the inside, in which case *the nasal surface of the hard palate must be covered by a few millimeters of palatal mucosa*. This is achieved by a soft tissue incision 4 to 5 mm toward the defect relative to the bony incision. The internal surface of the nares should be skin-lined to resist the abrasive effect of the retention arm of the prosthesis. Alternatively, retention is obtained using purely dental means, such as crowns, bars, and a removable partial denture (Fig. 9-7).

The cosmetic problems associated with anterior maxillectomy are compounded by resection and reconstruc-

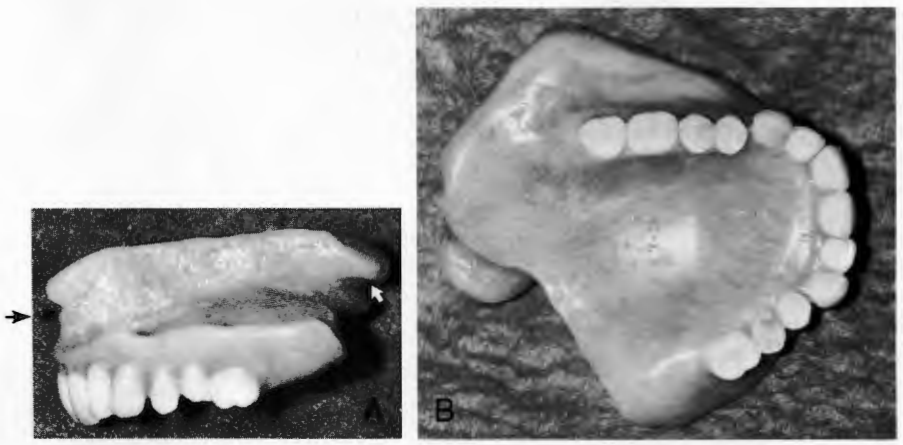

Figure 9-5. Maxillary prosthesis. (*A*) Lateral view. (*B*) Inferior view. The prosthesis is retained by means of a three-point undercut engagement: (1) posteriorly over the cut surface of the soft palate (*white arrow in A*), (2) laterally by the undercut created by the soft tissue scar band (shown in *B*), and (3) anteriorly by the floor of the nose (*black arrow in A*).

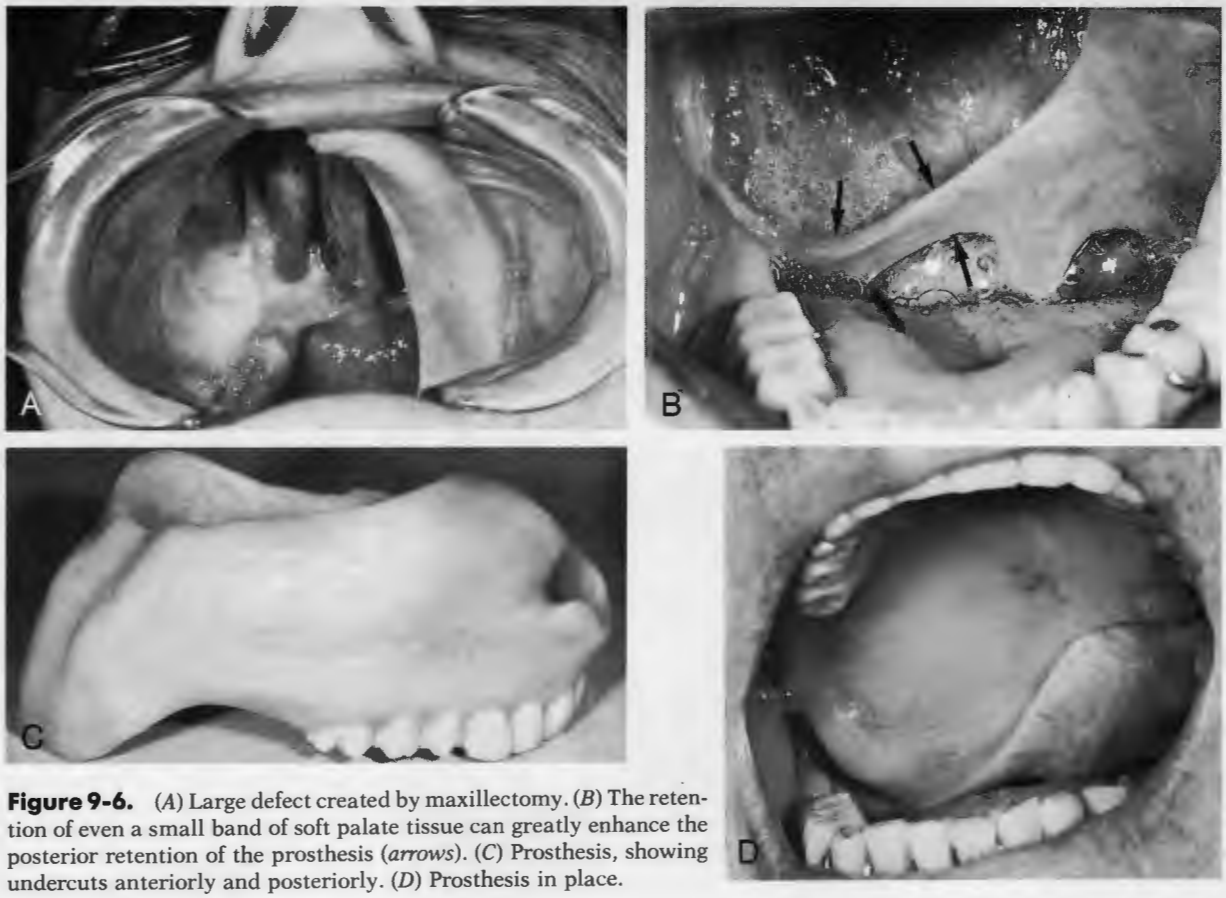

Figure 9-6. (*A*) Large defect created by maxillectomy. (*B*) The retention of even a small band of soft palate tissue can greatly enhance the posterior retention of the prosthesis (*arrows*). (*C*) Prosthesis, showing undercuts anteriorly and posteriorly. (*D*) Prosthesis in place.

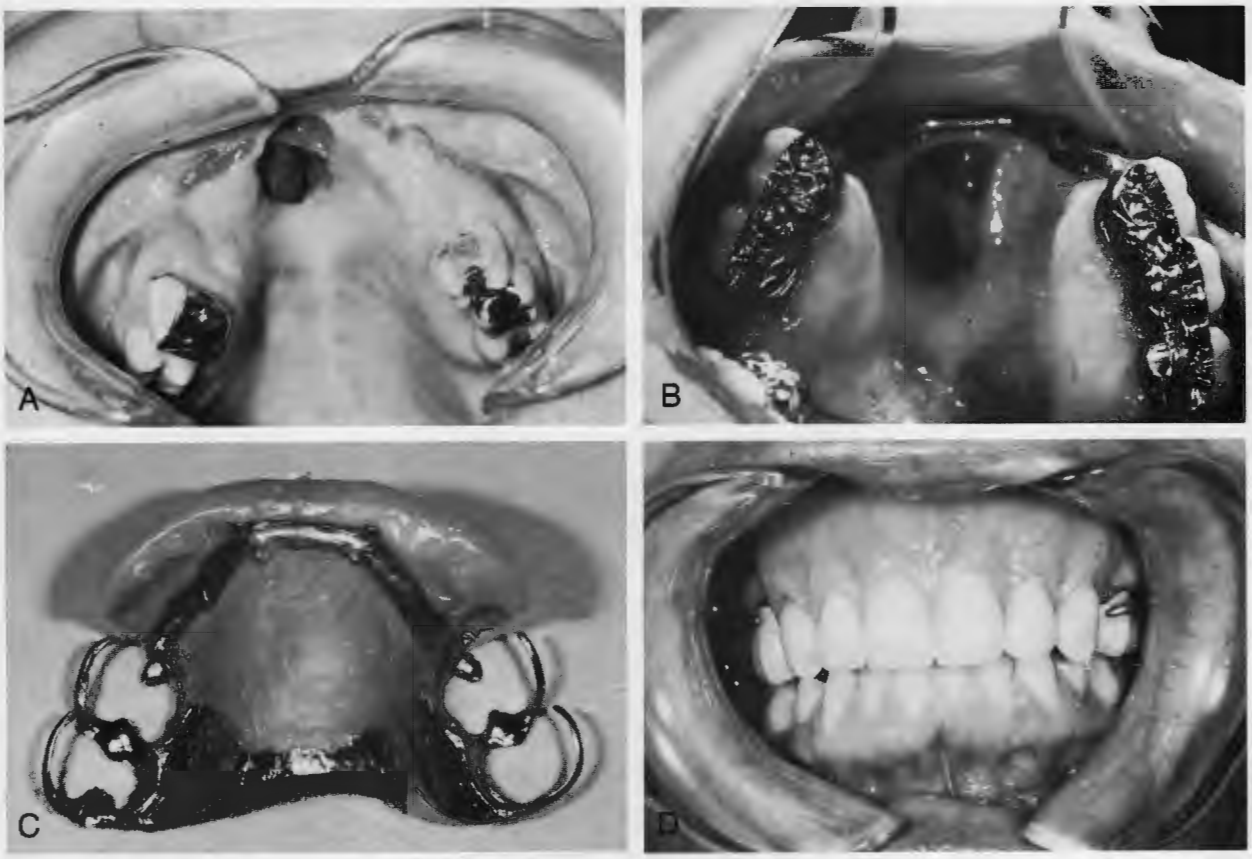

Figure 9-7. Restoration after anterior maxillectomy. (*A*) Maxillary defect. (*B*) Crowns and bar placed on teeth. (*C*) Removable partial dentures as a prosthesis for anterior maxillectomy. (*D*) Prosthesis in place.

tion of the lip. Use of dentures is also compromised by the lip resection.

Technical Aspects of Maxillary Obturator Construction for the Endentulous Maxilla

Surgical Prosthesis

The incision is outlined on the initial cast of the maxilla before the surgery. The area to be removed is smoothed down, and if patients have usable dentures, they can be modified for use as surgical prostheses. If not, the prosthesis is made from autopolymerizing acrylic resin directly on this modified cast to the outlined extensions. This is a simple 1-hour laboratory procedure. Teeth are not added at this stage. The primary object is to occlude the defect, separate the nasal from the oral cavity, and allow patients to begin oral feeding early in the postoperative period. This prosthesis remains in place 7 to 10 days, until the packing is removed. The prosthesis is highly polished to facilitate maintenance of oral hygiene.

Interim Prosthesis

In edentulous patients, the surgical prosthesis can be readily modified and used as an interim prosthesis. In a simple clinical procedure, an impression is made of the defect area. The prosthesis then is fashioned using autopolymerizing acrylic resin. It is refinished and polished for use as the interim prosthesis. At this stage, it may be necessary to correct the extensions of the prosthesis relative to the borders around the mouth, as well as the defect areas. The impression should record all of the undercut areas that will be used in the retention of the prosthesis.

PROSTHETIC RESTORATION AFTER MANDIBULECTOMY

The philosophy in treating patients who have had segmental mandibulectomy must be based on the priorities of function and cosmesis. Even if only the highest priorities can be satisfied by using a prosthesis, patients benefit significantly. Priorities, in order of importance, are swallowing and control of saliva, speech, cosmetic result, and masticatory efficiency.

Resection of a portion of the mandible usually is associated with soft tissue defects of the floor of the mouth and tongue. Prognosis for prosthetic reconstruction deteriorates rapidly with an increase in the amount of tissue removed. Problems after mandibulectomy without surgical reconstruction include a cosmetic defect, deviation of the mandible to the defect side, and a functional loss proportional to the amount of tongue and soft tissue removed. Surgical reconstruction of the bony mandible is preferable to prosthetic management. Surgical management restores the continuity of the mandible and greatly reduces facial distortion. Removal of a large amount of tongue tissue, however, may not allow restoration of normal speech by either surgical or prosthetic means. Even with greatly reduced tongue tissue, patients can learn to swallow.

When surgical restoration is not planned, prosthetic management must be instituted immediately. Placement of an inclined plane or guide flange prosthesis trains patients to center the mandible into the previous position of closure, minimizing facial distortion. The inclined plane prosthesis is modified during the healing phase to an interim prosthesis, and then, after healing, to a definitive prosthesis, which is used for cosmetic and functional purposes. This is done for both dentulous and edentulous patients, with proper provision to ensure adequate retention of the prostheses. In addition, exercises to reposition the mandible by use of hand pressure should be done three to four times per day. These exercises should begin 2 weeks after surgery, and should continue during radiation therapy and until a definitive prosthesis has been constructed. Patients must be taught and encouraged to use what is essentially a unilateral, lower, removable partial denture. The level of patient motivation is very important. The prosthesis may present major problems in stability and retention. The limitations of the prosthesis and patients' expectations should be honestly evaluated, and patients should be instructed on the best use of the prosthesis. It is essential that patients exercise and train themselves, using a mirror, to close and centralize the mandible properly.

Speech and swallowing problems arise after major tongue resection. A partially successful method of improving tongue function for both speech and swallowing is a palatal–tongue prosthesis. This involves lowering the palate with a thickened prosthesis to enable the remaining portions of the tongue to touch the palate and aid swallowing. Speech articulation involving the tongue and palate can also be improved in this manner.

Edentulous Mandible

In edentulous patients, the situation must be viewed in perspective: wearing a full lower denture is difficult even for edentulous patients who have an intact mandible. For patients who have had a mandibulectomy, greater potential difficulties exist. Prosthetic restoration after segmental mandibulectomy requires the construction of a complete denture on the reduced basal seat provided by the residual mandibular alveolus. The denture should not extend into the defect area where no bony support is available.

Little chance exists of regaining the preoperative level of function in edentulous patients after a mandibulectomy without surgical reconstruction. The reasons for this are decreased neuromuscular control resulting from denervation of the tissues surrounding the denture, decreased basal seat to support the denture, altered mucosal surface as a result of radiation therapy, altered saliva output with its higher mucin content, and altered pathway of mandibular closure after a partial mandibulectomy.

In summary, to ensure a favorable prognosis for prosthetic reconstruction after mandibulectomy, the following criteria should be present:

- Positive patient attitude with regard to prosthetic limitations
- Posterior segmental mandibular resection
- Minimal soft tissue and tongue resection
- Minimal deviation of the mandible after surgery
- No radiation therapy with resulting changes in saliva and mucosa
- Minimal cosmetic deformation as a result of surgery

Amount and location of the bony resection are the most important factors. The more posterior and the smaller the resection, the more favorable is the prognosis.

The use of osseointegrated dental implants holds great promise for providing a stable prosthesis for surgical patients. Implants require additional surgery for reconstruction, however. As the experience and success of dental implants increase for the normal population, the use of dental implants for reconstruction of surgical defects with implant-supported prostheses will also increase.

Dentulous Mandible

The same principles for restoration apply to dentulous patients as to edentulous patients, except that having teeth aids in the retention and stability of the prosthesis. Although the presence of teeth benefits both patients and prosthodontists, patients must maintain good oral hygiene in a difficult situation. The remaining teeth do not occlude normally and the mouth's self-cleansing mechanisms of the cheeks, floor of the mouth, and tongue are impaired.

To arrive at a realistic prognosis for dentulous patients, the same criteria are used as for edentulous patients, except that the prognosis can be improved slightly. When teeth are present and radiation therapy has been used as a treatment modality, however, the teeth are subject to more rapid deterioration than under normal circumstances. Preventive measures, such as daily topical fluoride application, should be instituted and maintained. Maintaining good oral hygiene cannot be emphasized enough to dentulous patients. This is essential for a favorable prognosis on the life span of the teeth and the prosthesis.

Surgical Reconstruction

Interaction between surgeon and prosthodontist is necessary to achieve optimal levels of rehabilitation for patients with acquired defects. For example, a mandibular rim resection was done to remove an anterior floor-of-mouth lesion. After the carcinoma was removed, the buccal vestibule was sutured to the lingual vestibule to cover the exposed bone. This produced excellent healing; however, the surgical site was almost impossible to restore with a prosthesis, since the tongue and floor of the mouth had become continuous with the cheek. Before prosthetic reconstruction could begin, a second surgery, or vestibuloplasty, using a skin graft had to be performed.

With preoperative interaction between surgeon and prosthodontist, surgery for cancer and reconstructive surgery can be performed during the same operation. For

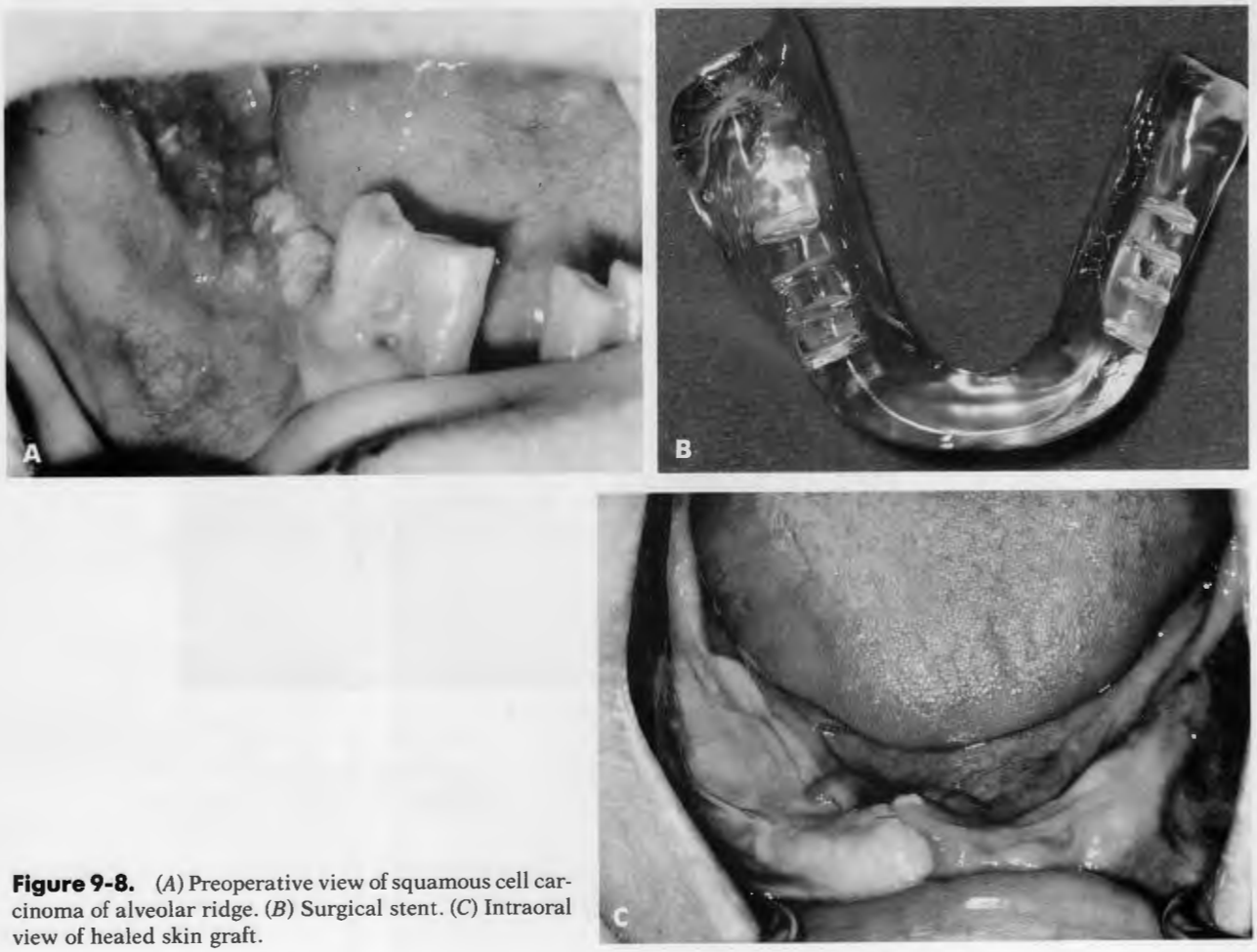

Figure 9-8. (*A*) Preoperative view of squamous cell carcinoma of alveolar ridge. (*B*) Surgical stent. (*C*) Intraoral view of healed skin graft.

Figure 9-9. (*A*) Panoramic roentgenogram of mandibular reconstruction with freeze-dried rib. Arrows point to connection of rib to remaining mandible. (*B*) Intraoral view of healed vestibuloplasty. (*C*) Mandibular prosthesis. (*D*) Prosthesis in place. (*E*) Full-face view. (*F*) Panoramic roentgenogram taken 4½ years postoperatively.

example, a patient with a diagnosis of squamous cell carcinoma of the mandibular right alveolar ridge was referred preoperatively to the maxillofacial prosthetic service for construction of a surgical stent (Fig. 9-8). The proposed surgery was a right mandibular rim resection and extraction of the remaining teeth. Postoperative radiation therapy was planned. The surgical stent was fabricated before surgery. In the operating room, after the tumor was removed and the skin graft had been sutured in place, the fit of the surgical stent was corrected by using modeling-plastic impression compound. This impression was relined with a soft lining material and ligated in place with circummandibular wires. When the stent was removed (10 to 21 days after surgery), the healed surgical site had attached mucosa on the superior portion of the mandible. This provided a stable base for a prosthesis without need for a second operation.

Surgical reconstruction after a hemimandibulectomy and radiation therapy is very challenging and requires several surgical procedures, as shown in Figure 9-9. Before surgery the patient was treated with hyperbaric oxygen. The body and ramus of the mandible were reconstructed using freeze-dried rib and autogenous corticocancellous bone. The vestibuloplasty was done as a separate procedure so that the blood supply to the bone graft was not compromised. After the skin graft had healed, a prosthesis was constructed, and the patient returned to his full-time job.

RESTORATION OF SURGICALLY INDUCED EXTRAORAL DEFECTS

Some basic requirements must be met for a facial prosthesis to be successful. The problems with artificial restoration of facial defects generally are two fold—attachment and camouflage. First, the area where the prosthesis will be attached must be retentive. Retention is achieved by engaging opposite undercuts with an elastic type of prosthetic material, or by having available a stable skin area to which the prosthesis can be attached by means of an adhesive. Ideally, a stable, retentive skin area is not oily, does not sweat, has no saliva flowing across it, and is not movable. The best method of obtaining such an area is by grafting skin onto a flat bony area.

The second problem is matching colors and camouflaging the borders or edges of the prosthesis. It is easier to restore the entire ear or nose prosthetically than a portion of a nose or ear. The remaining tissue generally is unstable and must be overlaid to integrate the prosthesis and to ensure stability and retention. This may increase the bulk of the prosthesis and interferes with its contour.

Auricular Prostheses

When the helix of the ear is surgically excised to remove a carcinoma and a prosthesis is planned, a preoperative consultation between the surgeon and the prosthodontist benefits patients. If the tragus can be left intact, it helps to hide the anterior margins of the prosthesis (Fig. 9-10). When the surgical site has stabilized, usually 2 to 4 months after surgery, an impression is made of the ear with the defect, as well as the normal ear. A wax sculpture is made to be a mirror image of the normal ear. This sculpture is tried on the patient, and modifications are made while the patient and one or more relatives observe. The prosthesis is then made. At the final appointment, extrinsic color is added to the prosthesis so that it blends with surrounding skin. An observer can see both ears only from a straight frontal view or a rear view. It is from these two perspectives that the prosthesis must look most like the normal ear.

Silicone rubber is the most commonly used material for extraoral prostheses because it has flexibility and texture similar to skin. The silicone rubber prosthesis is held in place using medical-grade skin adhesive. Patients can wear the prosthesis for several hours at a time without having to replace or add to the adhesive. The prosthesis is removed in the evening to expose the surgical site to the air.

Nasal Prostheses

The margins of the prosthesis for a partial rhinectomy defect or a total rhinectomy defect are placed for esthetics in the nasolabial folds bilaterally. For the partial rhinectomy, overlap may be added to the prosthesis to prevent placing the margin in the midline of the face. The prosthesis may be made from a rigid plastic or acrylic resin or from silicone rubber. Although acrylic resin is inflexible, it is very durable and can be attached to eyeglasses (Fig. 9-11). This has the disadvantage that the prosthesis is removed whenever the eyeglasses are removed. Acrylic resin prostheses do not need skin adhesives and are indicated for patients whose skin will not tolerate daily application of adhesives after radiation therapy.

Orbital Prostheses

The restoration of an orbital defect presents a special problem. The normal eye moves constantly, whereas the artificial eye has a fixed stare; the eyelids do not move and the gaze does not change direction. The orbital prosthesis can be camouflaged by means of eyeglass frames. Cosmetic success of an orbital prosthesis differs, however, from cosmetic success of a nasal or auricular prosthesis. All three prostheses appear natural in a photograph. In reality, however, ear and nasal prostheses appear lifelike, but the orbital prosthesis may not.

The orbital prosthesis is the most difficult to construct and may be poorly accepted by patients if the artificial eye, or ocular, does not accurately line up with the normal eye when patients are gazing straight ahead. A lack of alignment calls attention to the side with the defect, because during conversation it is normal to glance at the speaker's eyes. The proper placement must be verified at the second sculpting appointment. At the final appointment, the placement of the ocular is again verified, and patients are instructed to turn the head to the side when looking at an object so that the ocular tracks with the normal eye (Fig. 9-12).

Before construction of the prosthesis, patients should understand its cosmetic advantages and disadvantages. It is helpful if patients can talk with another patient who has had similar treatment. Demonstrations and audiovisual aids also are valuable.

(text continues on page 183)

Figure 9-10. (*A*) Postoperative view showing tragus and skin graft. (*B*) Prosthesis in place. (*C*) Full-face view showing both ears.

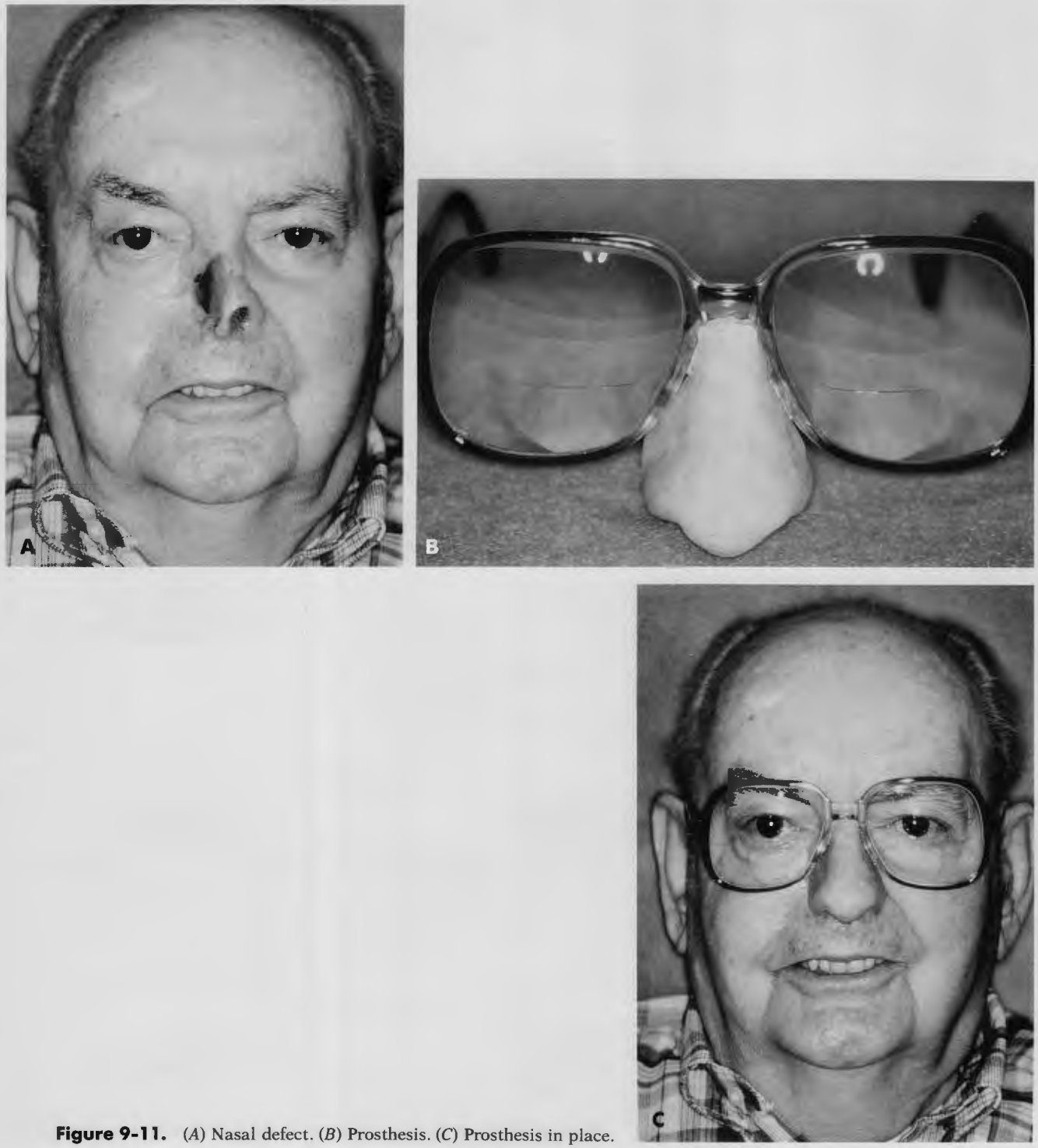

Figure 9-11. (*A*) Nasal defect. (*B*) Prosthesis. (*C*) Prosthesis in place.

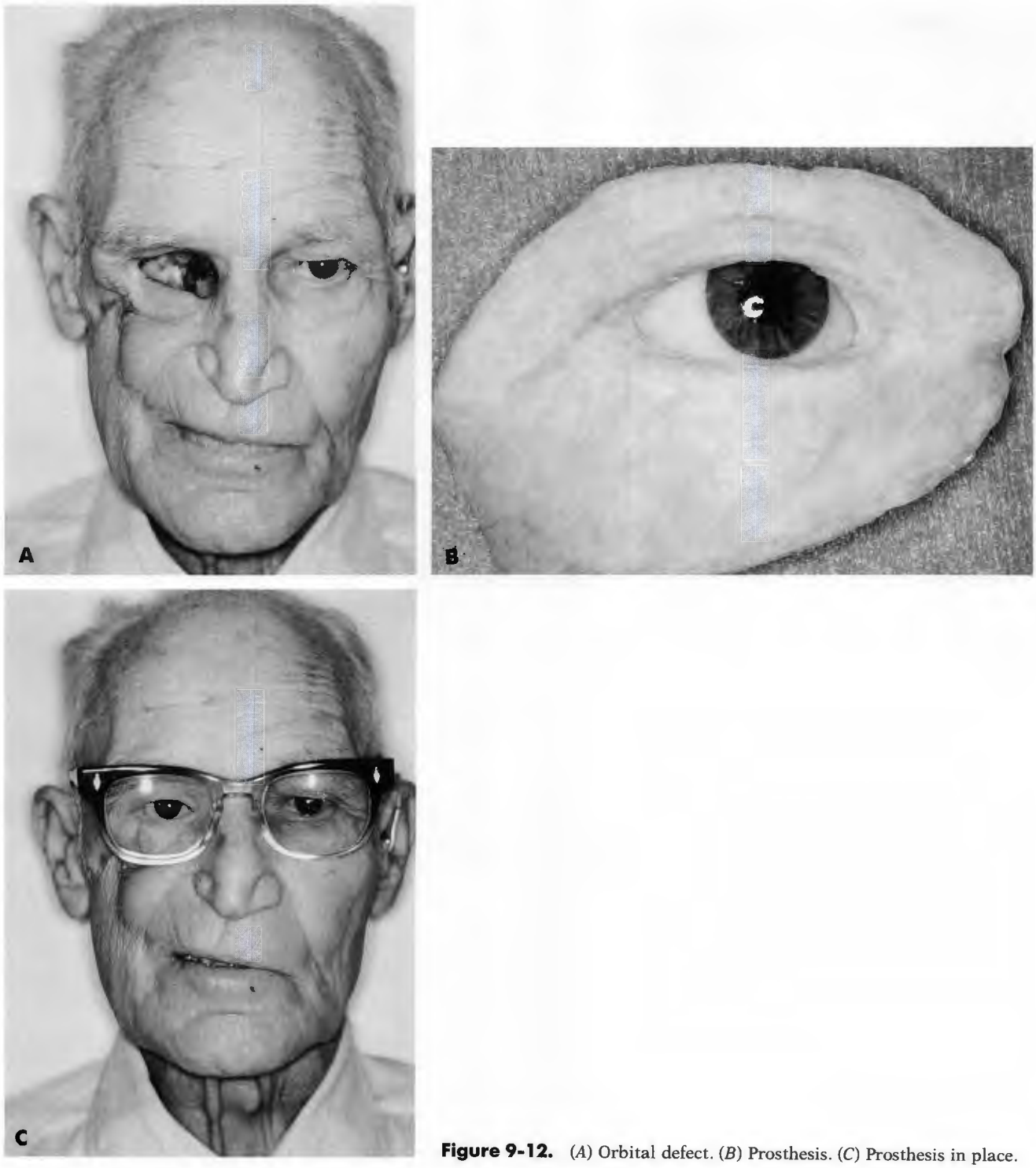

Figure 9-12. (*A*) Orbital defect. (*B*) Prosthesis. (*C*) Prosthesis in place.

Figure 9-13. (*A*) Intraoral view of four implants. (*B*) Tissue bar. (*C*) Tissue surface of obturator with two gold clips. (*D*) Prosthesis in place. (*E*) Full-face view.

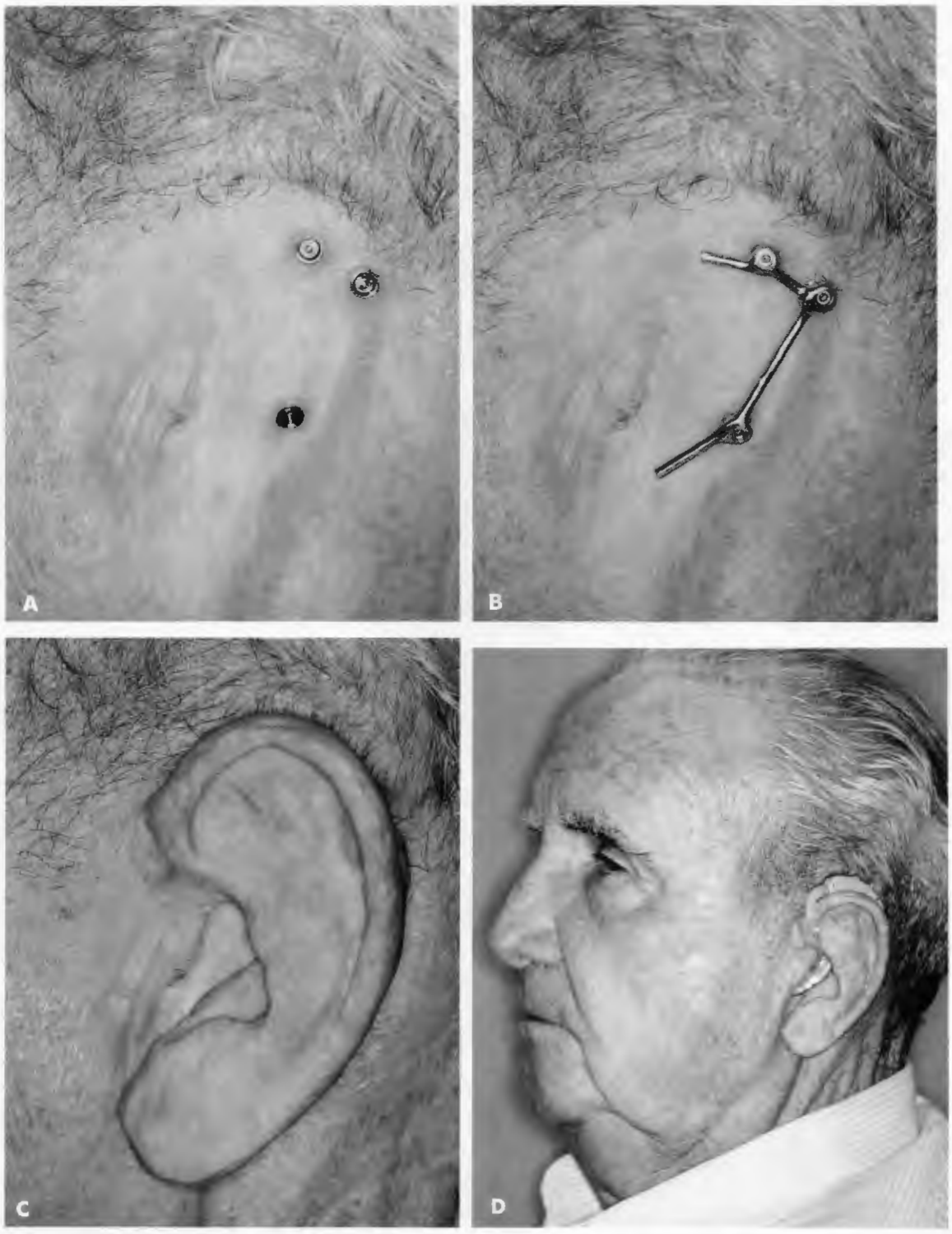

Figure 9-14. (*A*) Auricular defect with tragus, skin graft, and three implants. (*B*) Tissue bar. (*C*) Prosthesis in place. (*D*) Full-profile view showing prosthesis and custom-made hearing aid.

INTRAORAL AND EXTRAORAL IMPLANTS

Implants that are anchored in bone and penetrate mucosa or skin had a poor long-term prognosis in the United States before the 1980s, and few such implants were used for reconstruction of surgical defects before that time. A Swedish orthopedic surgeon, Dr. P.I. Branemark, introduced the term *osseointegration* to the United States. Osseointegration requires careful cutting of bone, because the temperature of the bone must not go above 47°C, and use of two-stage implant placement; that is, the first stage is buried under the soft tissue for 3 to 5 months before the second stage, which penetrates the mucosa or skin, is connected.

Branemark began the study of bone and soft tissue healing with animals in 1952 at the University of Gotenberg. In 1965, the first titanium screw implants were placed in humans. Branemark had more than 15 years of clinical data compiled in a university setting before his methods were disseminated in the United States. The data showed a more than 90% long-term success rate. June 1990 marked the 25th year of clinical success. The Branemark system of implants was the first to achieve approval by the American Dental Association.

These implants now are used in irradiated bone after patients have had hyperbaric oxygen treatment. The success rate in irradiated bone is reduced, but no instance of osteoradionecrosis has been reported. For nonirradiated patients, the use of implants holds tremendous promise to eliminate the need for adhesives and to securely anchor prostheses in place.

Intraorally, implants hold the prosthesis firmly and greatly improve mastication. For example, a patient had a hemimaxillectomy at 13 years of age for a chondrosarcoma. Fifteen years later she has had a bone graft to the maxillary sinus, four implants placed, a gold tissue bar constructed, and a maxillary implant-supported obturator constructed (Fig. 9-13).

The adhesives are the weakest aspect of extraoral prostheses. Because they are not dependable for more than a few hours at a time, patients may lack confidence that the prosthesis is securely in place. The use of implants that penetrate the skin to rigidly secure a prosthesis in facial or skull bones eliminates the use of adhesives for the successful implant patient.

Depending on the anatomy of the tissue and the quality of the bone, implants may be placed in nasal, orbital, and auricular defects.

An auricular defect with three implants penetrating the skin is shown in Figure 9-14. (Note that the tragus was maintained and a skin graft was performed at the time of the cancer surgery.) A gold tissue bar was constructed, and an implant-supported auricular prosthesis snaps onto the bar. The patient removes the prosthesis at night to clean the implant posts and to allow the skin to have contact with air. The patient can wear the prosthesis all day without fear that it will come loose during any activity. This patient had a custom-fitted hearing aid constructed to fit onto the prosthesis (see Fig. 9-14*D*). The implant-supported prosthesis can easily support hearing aids and eyeglasses.

Acknowledgment *I thank Mr. Lee D. Mintz, CDT, for his contributions in dental technology and photography for this chapter.*

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10

DENTAL AND ORAL CARE FOR THE HEAD AND NECK CANCER PATIENT

PAMELA L. SANDOW AND RONALD A. BAUGHMAN

ORAL COMPLICATIONS OF RADIATION THERAPY

A wide variety of oral complications, ranging from mild discomfort to serious debilitation, can occur secondary to therapy for head and neck cancer. Some of the more significant problems and their prevention or management are discussed in this chapter.

Mucositis

Mucositis is a general term used to describe a state of mucosal irritation that can include erythema, inflammation, ulceration, and infection. In radiation therapy patients, mucositis is initiated by direct cellular damage from ionizing radiation. The cellular damage in the oral mucosa occurs most dramatically at the level of the basal cell layer.[1] Because the maturation time is about 2 weeks for the basal cell layer, the effects of cellular damage or the onset of mucositis usually becomes evident in the second or third week of radiation therapy. The process persists for 3 to 6 weeks after therapy is completed. The severity of oral mucositis is dose dependent; however, bacterial, fungal, and viral infections, which commonly occur in patients undergoing radiation therapy, may compound the condition and add significantly to the patient's discomfort.

Xerostomia

Dry mouth, or xerostomia, creates significant morbidity for the patient and special therapeutic considerations for the health care provider. Severe xerostomia can cause difficulty in food processing and deglutition and can result in significant oral discomfort after radiation therapy to the head and neck areas. When major salivary glands are irradiated, they can be partially or totally destroyed, resulting in permanent salivary dysfunction. Both the quantity and quality of saliva are altered. The serous component of salivary flow is affected most often, resulting in the production of saliva with a thick, ropy consistency. Decreased salivary protein content and buffering capacity compromise the xerostomic patient's ability to control oral microbial proliferation.[8] This phenomenon can initiate or exacerbate periodontal disease and chronic oral infections and can contribute to the development of radiation caries with possible progression to bone necrosis.

Infections

Patients undergoing head and neck radiation therapy have a dramatic increase in the incidence of oral colonization of *Candida albicans*.[6] Candidiasis can cause mucosal irritation and is often confused with radiation-induced mucositis. Bacterial and viral organisms, particularly herpetic viruses, can also produce significant discomfort and pain for the patient. These infectious processes should be monitored and treated during radiation therapy and also at posttherapy follow-up visits.

Increased Caries Rate

Severe dental caries results from the reduction in salivary flow, the decrease in salivary pH, and the proliferation of cariogenic bacteria in the oral cavity of the irradiated patient. This serious and sometimes debilitating

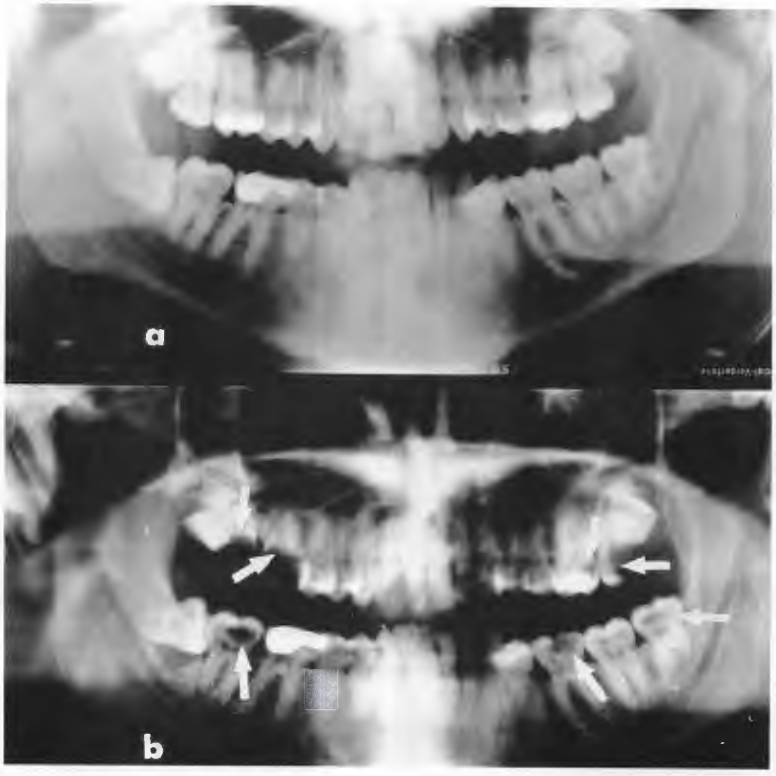

Figure 10-1. (*a*) Pantomographic film taken immediately after the completion of radiotherapy in a 23-year-old man treated for nasopharyngeal carcinoma. (*b*) Film of the same patient taken 24 months later. The patient did not comply with the use of daily topical fluoride applications. Advanced carious lesions are visible (*arrows*).

condition can lead to total destruction of the teeth and eventual loss of major segments of bone. The carious process in these patients can be rapid and is often detectable within a few months after radiation therapy is completed (Figs. 10-1 through 10-4). In most patients, this serious sequela can be eliminated or reduced with proper preventive care.

Osteonecrosis

Osteonecrosis can be associated with high-dose radiation therapy in the form of external-beam irradiation or iridium implants. Bone death is thought to occur primarily because of vascular insufficiency rather than infection of the bone.[10] Postirradiation osteonecrosis is often painful

Figure 10-2. Beginning radiation caries in the cervical areas of teeth.

Figure 10-3. Advanced carious destruction secondary to radiation-induced xerostomia.

Figure 10-4. Total destruction of teeth secondary to radiation caries.

and debilitating and can result in eventual loss of significant portions of the mandible or maxilla. The mandible is more frequently affected than the maxilla because of its alveolar prominences, moderate vascularity, thin mucosal epithelium, and trauma from the mobility of the tongue.

Trismus

Fibrosis of the muscles of mastication can occur secondary to high doses of radiation to the oral and facial regions. Consequently, limited opening of the mouth can make routine dentistry difficult or impossible. Patients experience difficulty in eating certain foods when opening is limited. With appropriate jaw exercises, this side effect can be minimized or sometimes totally eliminated.

Dysgeusia

Dysgeusia, or alteration in taste perception, is a common acute complication of therapeutic irradiation of the oral cavity. Most taste loss is recovered in 4 months, but some patients may experience permanent alteration.[7] A serious consequence of dysgeusia is loss of appetite leading to poor nutrition.

Hypoalimentation

Dysgeusia, combined with xerostomia and mucositis, seriously impedes the patient's ability to obtain proper nutrition. Special diets and nutrition counseling may be required to ensure an adequate nutritional state for patients in their debilitation during radiation therapy. Some individuals with xerostomia or postsurgical problems require long-term nutrition counseling.

ORAL COMPLICATIONS SECONDARY TO CHEMOTHERAPY

Chemotherapy is used to treat a limited number of head and neck cancers. The cytotoxic effects of chemotherapeutic drugs contribute to oral morbidity, including mucositis, xerostomia, increased caries rate, and infection. These tissue changes are similar to those induced by radiation. The oral health of a chemotherapy patient is severely compromised, and life-threatening septicemia can result from untreated oral infections and diseased teeth. Therapy-induced thrombocytopenia can be a serious problem when emergency or routine dental therapy is performed. Complications such as uncontrolled hemorrhage and infection are more likely to be life threatening in a chemotherapy patient than in a radiation therapy patient. In a chemotherapy patient, however, xerostomia and an increased caries rate are transient conditions. Salivary flow and composition should return to normal shortly after chemotherapy has ended.

The chemotherapy patient should be evaluated by a dentist before induction of chemotherapy to identify and eliminate potential sources of septicemia before the patient becomes granulocytopenic. These infections could include abscesses associated with devitalized teeth, carious teeth, and bony or soft tissue abnormalities that may not be obvious on cursory clinical examination.

ORAL CARE FOR THE RADIATION THERAPY PATIENT

Because many of the radiation-induced effects on the soft and hard tissues of the oral cavity are permanent, several precautions should be taken before the initiation of radiation therapy to ensure that these patients will have continued oral health for the remainder of their lives. Patients who require special dental and oral considerations are those who have the maxilla, mandible, or major salivary glands in the proposed fields of irradiation.

Pretherapy Dental Evaluation

When any major salivary glands are to be included in the treatment field, a dental evaluation is important even though the primary tumor is located outside of the oral cavity. When the proposed radiation therapy field includes bone of the mandible, maxilla, or teeth, a pretherapy dental evaluation becomes mandatory.

A dental evaluation, including radiographs, should be scheduled for both dentulous and edentulous patients immediately after the determination that oral structures or major salivary glands will be included in the field of irradiation. Intrabony pathology, impacted teeth, odontogenic infections, caries, and the periodontal status of the patient may not be obvious on clinical examination alone. Therefore, the evaluation should include a panoramic dental film and necessary intraoral radiographs, as determined by the dentist. The pretherapy radiographs, oral examination, and dental evaluation also serve as a baseline reference for future evaluation of the patient's oral condition.

Communication between the radiation oncologist and the dentist before radiation therapy begins is essential to ensure the best possible patient care. Before the dentist

is able to make appropriate dental recommendations, whether before or after radiation therapy, he or she must have information about the location of the field to be irradiated; dose to the oral soft tissues, bone, teeth, and related structures; other intended treatment modalities; and the diagnosis and general medical prognosis of the patient. Conversely, the radiation oncologist should be informed of any dental recommendations before they are instituted to prevent interference with the radiation therapy treatment plan and to minimize complications secondary to radiation therapy, such as radiation caries and osteonecrosis.

Edentulous Patients

To minimize oral infections, patients with existing prostheses should be instructed in proper denture care and oral hygiene before the start of radiation therapy. Dentures should be soaked in a fresh denture-disinfecting solution each day. Rough or sharp areas on the dentures should be eliminated to reduce the incidence of oral discomfort and possible tissue breakdown. Patients should be discouraged from wearing dentures throughout the duration of radiation therapy if bone of the mandible or maxilla is included in the high-dose treatment field. Limited use of dentures for eating or special social occasions is permissible as long as open ulcerations are not evident.

Dentulous Patients

Patients with teeth in the proposed high-dose treatment field have special dental considerations. The incidence of bone exposure and necrosis is greater in dentulous than edentulous patients.[13] The risk of bone necrosis increases with radiation dose, the amount of bone irradiated, and the overall health of the patient's teeth. Doses of less than 5000 cGy given over 4 to 5 weeks would rarely cause a serious bone necrosis, but the risk increases gradually above this level. Because of the serious consequences of osteonecrosis, it is recommended that teeth in poor condition be extracted, with 14 to 21 days allowed for healing before high-dose radiation therapy is instituted.[11,15]

Teeth with questionable prognosis—whether due to caries, periodontal disease, apical pathology, or unsatisfactory endodontic treatment—should be extracted. Periodontal disease resulting in bone loss in the furcation of the tooth or abnormal periodontal sulcal depths (generally more than 5 mm) can more seriously affect the long-term prognosis of the tooth than does the carious process. Bony defects secondary to periodontal disease cannot be restored to original health, and the proliferation of destructive microorganisms in the defects results in further bone resorption and eventual loss of the tooth. In addition, teeth in the proposed high-dose treatment field should be extracted if a state of good dental health cannot be maintained throughout the remainder of the patient's life. The age of the patient and the history of resistance to periodontal disease and caries should be taken into consideration in the pretherapy evaluation. Other indications for pretherapy extractions include nonrestorable teeth, teeth that are unopposed, and teeth that will require extensive restorative procedures in a patient with limited finances.

Patients with a low probability of cure should not be excluded from the pretherapy dental examination. In these patients, teeth with gross decay, severe periodontal disease, a history of pain, or radiographic pathology should be extracted before the initiation of radiation therapy even if the patient's life expectancy is short. This precaution allows the patient to have better quality of life without the added misery of dental pain.

Patients with excellent dental and periodontal health can retain their dentition if they are committed to dental examinations every 3 to 6 months, if they comply with the daily use of prescription fluoride, and if they maintain scrupulous oral hygiene. Before treatment, however, these patients should be informed of the possible risks of retaining teeth in irradiated areas if they do not comply with dental recommendations, particularly the daily use of fluoride. All pretherapy dental recommendations and discussions with the patient should be thoroughly documented.

When pretherapy extractions are indicated, teeth should be removed with as little trauma as possible. At the time of extraction, all areas of sharp bony projections should be eliminated, and preprosthetic alveoloplasty should be completed. Primary closure should be attained if adequate residual mucosa remains. Eventual mucosal breakdown can occur if the tissue is stretched beyond its physiologic limitations to achieve primary closure. The mylohyoid ridge is a common location of mucosal breakdown with subsequent development of osteonecrosis, and therefore, extreme caution should be used when extracting mandibular molars. Postextraction antibiotic coverage is recommended to reduce the incidence of postoperative infection and possible delays in radiation therapy.[3]

A dental débridement is recommended before the start of radiation therapy to help reduce the number of microorganisms and the incidence of oral infection. The pretherapy dental visit is also an appropriate time to counsel patients on oral hygiene procedures and the management of future xerostomia with its limitations on the ability to maintain oral health. Caries susceptibility, food impaction, and plaque accumulation increase the effort required to maintain good oral health in the xerostomic patient. Patients need constant long-term motivation from the dentist and radiation oncologist if oral health is to be maintained.

The pretherapy dental visit provides an opportunity to make impressions for fluoride carriers, thus allowing adequate time for the carriers to be prepared while the patient is receiving radiation therapy. The custom vinyl fluoride carriers (Fig. 10-5) can be fabricated using stone models of the patient's teeth and a vacuum-tray forming unit. In patients with extensive metal restorations, the carriers should be worn during treatment, without fluoride, to eliminate contact between the metal restorations and oral tissues, thereby reducing acute radiation reactions.

If necessary, routine dental procedures, including amalgam and composite restorations, dental radiographs, and nonsurgical endodontics, may be completed before or during radiation therapy, but should not postpone the initiation or continuation of radiation therapy.

Oral Care During Radiation Therapy

Mucositis is one of the most debilitating side effects of radiation therapy to the oral cavity. This phenomenon occurs as a result of direct radiation toxicity to the epithelium with development of mucosal inflammation, ul-

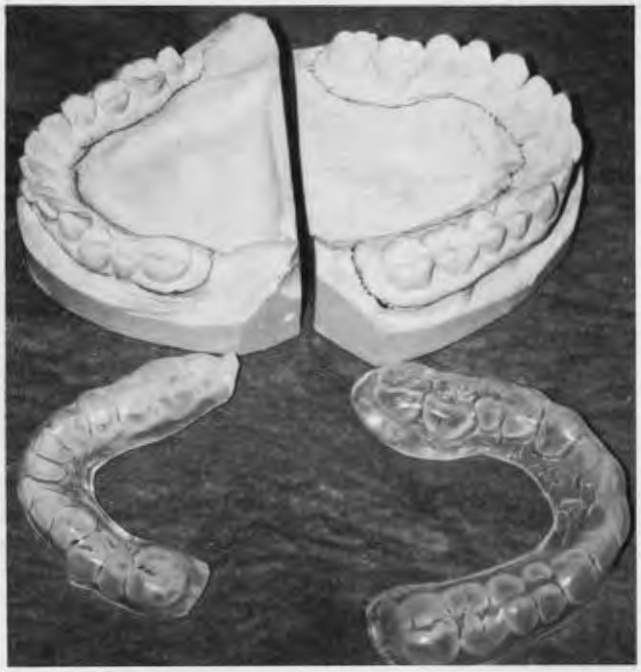

Figure 10-5. Custom vinyl fluoride carriers fabricated using stone models of the patient's teeth and a vacuum-tray forming unit.

cerations, or both. Bacterial, fungal, and viral infections can secondarily infect areas of existing mucosal ulceration. Clinical signs of oral candidiasis are common during radiation therapy to the oral cavity; however, organisms can persist long after radiation therapy is completed. The recommended treatment is the topical use of a broad-spectrum antifungal agent such as clotrimazole or fluconazole. A mouth rinse of 0.12% chlorhexidine has been effective in reducing the number of intraoral organisms, including *C albicans*, in patients undergoing other forms of cancer therapy. Further studies are needed to fully document its effectiveness in patients undergoing radiation therapy of the head and neck.

The patient is encouraged to maintain excellent oral hygiene during radiation therapy to decrease the incidence and severity of intraoral infections. A commercially available supersoft toothbrush, foam-tipped swab, or oral irrigation device may be used by the patient to facilitate oral hygiene during times of mucositis. Toothpaste specially formulated for children can be helpful in reducing the burning sensation that often occurs with the use of adult toothpaste.

Several remedies have been suggested for palliation of mucositis. A freshly prepared solution of 1 teaspoon baking soda and ½ teaspoon salt to a quart of water can temporarily ease pain in patients with mild to moderate mucositis. Unflavored 2% lidocaine (Xylocaine Viscous) used as a mouth rinse before eating can reduce pain, thereby enabling the patient to eat and obtain proper nutrition. Aspirin-containing chewing gum, which is frequently used by patients during radiation therapy, can be caustic to the tissues and increases the risk of tooth enamel destruction, and should be used sparingly. Foods that are acidic or spicy in nature or rough in texture should be avoided when the oral mucosa is inflamed or ulcerated. Alcohol, tobacco, and commercial mouth rinses should also be avoided at this time. The use of sugarless candy and gum often stimulates salivary production and lubricates irritated oral tissues.

Care After Radiaton Therapy

The radiation dose to salivary glands that induces xerostomia has been established (see Chap. 13); however, no literature has established a minimum radiation dose for induction of radiation caries. Sufficient evidence exists to conclude that the quality of saliva produced by irradiated salivary glands can be altered even when salivary flow approaches normal levels. Cariostatic salivary proteins that are decreased as a result of irradiation include lactoferrin, salivary peroxidases, surface immunoglobulin A, and immunoglobulin G.[8] Therefore, to prevent possible radiation caries, all dentulous patients with irradiated salivary glands (regardless of dose) should apply a neutral 1% sodium fluoride or 0.4% stannous fluoride daily in customized fluoride carriers (Fig. 10-6).

In addition to the prevention of decay, fluoride applications can minimize dental sensitivity experienced by some patients after radiation therapy. Daily use of fluoride should begin no later than 1 month after radiation therapy is completed, allowing time for mucosal ulcerations to resolve. Patients should be given instructions, both spoken and written, in the proper use of daily topical fluoride. The recommended procedure is as follows:

1. Brush and floss the teeth to remove all plaque.
2. Spread a thin layer of fluoride on the internal surfaces of the carriers.
3. Place the carriers on the teeth for 5 minutes, preferably at bedtime.
4. Remove the carriers and expectorate the residual fluoride.
5. Rinse the carriers in cold water and store in a clean, dry container.
6. Do not rinse, eat, or drink for at least 30 minutes after the fluoride application.

To ensure the preservation of the teeth, this procedure should be repeated *daily on a permanent basis*, regardless of the dose of radiation to the salivary glands.

Figure 10-6. Custom fluoride carriers as they appear when inserted in patient's mouth.

The development of radiation caries usually stems from the failure of patients to use prescribed topical fluoride for the remainder of their lives because of a lack of motivation or understanding of its importance. Patients may discontinue the use of fluoride because they believe that no changes are occurring as a result of its use. Patients should be informed that no changes should occur in their teeth if the fluoride is used properly. If the patient does exhibit areas of cervical or occlusal decay or demineralization of enamel, it is an indication that fluoride is not being used properly, and the patient's fluoride regimen should be evaluated. The most common errors in the use of fluoride include (1) use of fluoride for less than the recommended period of 5 minutes each day, (2) failure to eliminate plaque from teeth properly before fluoride is applied, (3) rinsing mouth with water or eating too soon after fluoride is applied, and (4) discontinuation of the use of fluoride after several months or years. The dentist and radiation oncologist, as a team, are responsible for motivational reinforcement at follow-up visits throughout the posttherapy years.

Management of xerostomia in post–radiation therapy patients often provides only temporary relief. Various nonprescription saliva substitutes are available, but patient acceptance of these products is usually low. In our experience, the most consistently used therapy is frequent, intermittent sips of water. Some patients benefit from the use of sugarless candy, gum, or carbonated sodas. Patients should avoid commercial mouthwash because of its alcohol content and tendency to desiccate the oral tissues. Most patients must alter their diets by adding liquids to foods that are low in moisture. A room humidifier may facilitate the patient's ability to sleep at night. Water-based lubricants can be applied to lips to help prevent chapping. Pilocarpine has been used effectively in some post–radiation therapy patients when residual functional salivary gland was present; however, the drug is not available in the United States for use as a sialogogue, pending Food and Drug Administration approval. Recent reports of electrostimulation of salivary glands have promoted interest in that area. Additional studies are required before the therapy can be properly assessed for effectiveness in post–radiation therapy patients.

Most routine dental procedures may be performed safely and should be encouraged in the years after head and neck radiation therapy. Radiographs should be an integral part of follow-up dental evaluations of post–radiation therapy patients. The small amount of radiation added by dental radiographs is inconsequential in comparison with therapeutic doses. Dental therapies that are potentially dangerous because of the risk of osteonecrosis include extractions and periodontal surgery if they expose bone in areas that have received high-dose irradiation. Teeth in bone receiving 5000 cGy or less can generally be removed with minimal risk of osteonecrosis.[3,5,13] Radiation-induced tissue damage is a function of dose, fractionation, field location, and form of ionizing radiation; therefore, these variables need to be evaluated with the radiation oncologist before any extractions are performed in the radiation therapy patient. When extractions are contraindicated, nonsurgical endodontics is recommended as the conservative treatment for teeth with odontogenic infections or extensive caries. Careful instrumentation of the root canals is required to prevent extrusion of medicaments beyond the root apices. Advanced carious lesions in teeth that are nonrestorable may require the dentist to level the tooth to the gum line, leaving the roots in bone. The retained roots often exfoliate over time, causing minimal trauma to irradiated tissues.

In the edentulous or partially edentulous patient, the timing of placement of removable dental prostheses over irradiated bone is controversial. The risk of osteonecrosis in edentulous patients is considerably less than in dentulous patients. However, ill-fitting prostheses may cause mucosal irritation and ulceration, possibly progressing to osteonecrosis. Post–radiation therapy patients should be instructed to remove prostheses immediately if ulcerations develop. The risk of osteonecrosis is minimal in patients who have prostheses before the start of radiation therapy. Patients with existing dentures should wait for mucosal healing after radiation therapy before wearing their appliances. It has generally been recommended that patients requiring extractions before radiation therapy wait 6 months to 1 year before having dentures placed.[4,14] However, some maxillofacial prosthodontists have had good results when placing prostheses as soon as the oral tissues have returned to a normal appearance.

Normal alveolar bone undergoes a process of remodeling after extractions. This natural phenomenon of bone formation and resorption results in smooth bony contours after several months. Cancer-destroying doses of radiation seriously inhibit this process, thereby resulting in an irregular alveolar ridge if alveoloplasty is not performed at the time of extractions. The previous recommendation for delaying prosthetic placement is based on this factor as well as on the need to give soft tissues sufficient time to recover from the effects of radiation. However, the prosthodontist should assess each patient on an individual basis for tissue health and contours before the determination of denture prosthesis placement.

HYPERBARIC OXYGEN

Hyperbaric oxygen (HBO) therapy is used to prevent the initiation of bone necrosis in patients requiring surgical procedures in bone that has received high-dose irradiation. It is also used in patients with clinical manifestations of osteonecrosis to prevent further progression of bone necrosis. HBO therapy has been shown to promote angiogenesis, cellular proliferation, and collagen synthesis in hypovascularized irradiated bone and soft tissue.[2]

Complications that occur during HBO therapy occasionally include claustrophobia, ear or sinus damage, or tympanic membrane rupture from inability to equilibrate air spaces after changes in barometric pressure. Pneumothorax, air embolism, and oxygen toxicity are rare complications. Overall, it has been demonstrated that HBO is safe therapy for individuals with irradiated tissues.[9]

In the absence of bone necrosis, the established protocol for extractions, minor oral surgery, or major jaw reconstructive surgery in irradiated tissue consists of 20 sessions (dives) of HBO therapy preoperatively and 10 dives postoperatively. (Each dive consists of inhalation of 100% oxygen at 2.4-atm absolute pressure for 90 minutes.) In some circumstances, preextraction HBO therapy may not be readily available for patients with nonrestorable or painful teeth that have been included in the high-dose irradiation field. In these cases, the teeth should be endodontically treated to alleviate the pain. If the tooth is nonrestorable, the crown may be removed

and smoothed level with the gum line, leaving the roots retained in bone. The root tips should eventually exfoliate without trauma and with negligible risk of osteonecrosis. It is difficult to make a blanket statement as to when a patient should be referred for HBO therapy when evidence exists of early osteonecrosis or bone exposure. Many times, small areas of exposed bone sequester and heal without complication. It is generally accepted that a patient with a bone exposure that persists for longer than 6 months without improvement would be a candidate for HBO therapy. If, however, there are signs of rapidly expanding areas of necrosis including suppuration or radiographic evidence of osteonecrosis, it is prudent to recommend HBO therapy.

When the clinical manifestation of osteonecrosis is present, the recommended treatment is 30 dives of HBO therapy. The progression of healing should be monitored at intervals throughout the course of this therapy. For small bone exposures, which include very early stages of osteonecrosis, 30 dives may be all that is required for wound healing. However, surgical débridement of nonvital bone and primary closure of the wound are necessary to facilitate normal healing in the more advanced stages of osteonecrosis. An additional 10 postoperative dives are often necessary for complete resolution of the wound.[12]

MANAGEMENT OF HEAD AND NECK SURGERY PATIENTS

A team approach optimizes the chance of rehabilitating a patient who undergoes head and neck surgery. Before therapy, the surgeon and maxillofacial prosthodontist should collaborate to ensure preservation of tumor-free anatomic structures, including teeth. These structures will help with proper retention of prosthetic appliances later. The maxillofacial prosthodontist can provide a broad spectrum of functional and cosmetic replacements to facilitate the patient's total rehabilitation (see Chap. 9). Patients requiring surgery and postoperative radiation therapy can benefit from coordination among the head and neck surgeon, radiation oncologist, and dentist. Dental extractions required before the start of radiation therapy can be performed at the time of the head and neck surgery, eliminating an additional traumatic surgical experience for the patient. An added advantage to this procedure is that additional time is available for the extraction sites to heal completely before radiation therapy begins.

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11

NUTRITIONAL MANAGEMENT IN PATIENTS WITH HEAD AND NECK MALIGNANCIES

EDWARD M. COPELAND III AND LEE M. ELLIS

Surveys of protein-calorie malnutrition in major metropolitan hospitals have indicated that 40% of malnourished, hospitalized patients have cancer.[3] Malnutrition is harmful to cancer patients because the cachectic patient has a narrower safe therapeutic margin for most oncologic therapy. In the malnourished patient, the increased risk of complications secondary to undernutrition can limit the dose of oncologic therapy, and the patient may not be classified as a reasonable treatment candidate even though a potentially responsive malignant lesion exists. Radiation therapy, chemotherapy, and surgery predictably increase the nutrient requirement and, at the same time, interfere with the patient's ability to eat. Consequently, malnutrition often results from the intensive effort to eradicate the tumor by a combination of these treatment modalities.

Patients with head and neck malignant neoplasms present special nutritional problems because they often have a history of smoking, dietary indiscretions, and high intake of alcohol. They may be undernourished and have vitamin deficiencies. Malnutrition may be potentiated by the anatomic location of the cancer if it results in obstruction or pain on deglutition. Protein-calorie malnutrition results in impaired wound healing, reduced immunologic function, increased susceptibility to infection, and decreased tolerance to effective oncologic therapy. Clinical and experimental studies have demonstrated that nutritional repletion before or during oncologic therapy restores immunologic function to normal[11] and reduces preoperative mortality and morbidity.[22,25]

Based on the studies to date, both retrospective and prospective, nutritional repletion should be a goal in the malnourished cancer patient through the use of dietary supplements, tube feeding regimens, total parenteral nutrition (TPN), or a combination of these. The practicing oncologist must recognize the malnourished patient who presents for cancer therapy, be able to initiate measures to replenish the patient before proceeding with therapy, and attempt to prevent further nutritional depletion during treatment.

SELECTION OF TREATMENT

A set of complex tests is not usually necessary for the diagnosis of malnutrition. If the physician knows the initial nutritional state of the patient and the magnitude of the nutritional problem likely to result from the planned oncologic therapy, then the need for nutritional supplementation can be predicted. Unfortunately, the physician does not always have the luxury of waiting until nutritional repletion is complete before beginning cancer therapy, and the risk of waiting too long to initiate oncologic therapy may outweigh the benefits of prolonged attempts at nutritional rehabilitation.

The practicing physician cannot always do all available nutritional assessment tests. Because amino acids are distinguished from other nutrients by the presence of nitrogen, nitrogen balance is appropriately used as a nutritional index to indicate if the calorie and nitrogen delivery is adequate. A simple way to calculate the calorie and protein needs as an initial starting point is to supply calories at 35 kcal/kg/d. Occasionally a greater caloric delivery may be necessary to initiate anabolism in a malnourished patient. Nitrogen (protein in grams divided by 6.25) should be given at a ratio of about 1 g per 120 to 150 nonprotein calories (about 2 g/kg/d protein).

Patients who are incapable of adequate enteral nutrition because of previous oncologic therapy are candidates for nutritional rehabilitation with TPN. Infrequently, healthy patients whose treatment plan necessitates multiple courses of chemotherapy, possibly combined with radiation therapy or surgery, and in

whom these treatment modalities predictably result in malnutrition, should be considered for nutritional supplementation with TPN if all attempts at oral alimentation fail.

Low serum albumin concentration (less than 3.4 g/dL) and loss of delayed cutaneous hypersensitivity are late manifestations of malnutrition. The return of these indicators to normal during nutritional rehabilitation is slow. For this reason, nutritional support teams have used other indices, such as serum concentrations of prealbumin, retinol-binding protein, and transferrin, because the half-life of each these compounds is shorter than that of albumin. A rise during nutritional rehabilitation may indicate the conversion of patients from a catabolic to an anabolic state.

The method of feeding patients depends on the treatment modality and the initial nutritional status of the patient. Attention to nutritional status at the initial interview and appropriate dietary counseling results in nutritional rehabilitation of most patients. Oral feedings should be the ultimate goal. Standard hospital diets plus oral supplements or tube feedings with defined formula diets should be ordered for patients who are initially in good nutritional status. However, delivery of nutrients to the gut does not always result in nutritional restoration of the starving patient because the syndrome of malnutrition may include malabsorption. In severely cachectic individuals, the gastrointestinal columnar mucosal cells become cuboidal and the brush border is reduced in height. There is a decrease in production of mucosal cells and a decrease in migration from the crypts. Gastrointestinal motility diminishes, and overgrowth of facultative and anaerobic bacteria results. These morphologic, absorptive, and bacteriologic abnormalities of the gastrointestinal tract in the malnourished patient are reversible after protein-calorie replenishment. The process is slow, however, because adequate enteral nutriments are initially partially malabsorbed and uncomfortable symptoms of nausea, diarrhea, abdominal pain, and bloating limit the patient's desire to eat.[34]

Data from our laboratory suggest that glutamine supplementation in defined formula diets may more rapidly restore the function of the small bowel mucosa.[19,32] Glutamine is the major fuel for enterocytes, and its absence from the diet results in mucosal atrophy and a breakdown in the mucosal barrier. Glutamine may be supplied by either the enteral or the intravenous route but is not yet approved for inclusion in the amino acid formula for TPN. Therefore, during TPN, if the gut is available for nutrient delivery, it should be utilized, and preferably by formulas that contain glutamine, even if the volume delivered is small.

Seniukov and associates[31] reported an evaluation of the efficacy of TPN used perioperatively in malnourished patients with carcinoma of the larynx. Seventy patients received TPN and 90 patients were fed through nasogastric feeding tubes. The two groups of patients were selected carefully to be matched for stage of disease and for dose of preoperative radiation therapy. Primary wound healing occurred in 75% of the TPN-fed group versus 40% of the enterally fed group. Ten percent in the parenteral group developed pharyngeal fistulas compared with 29% in the enteral group. Nevertheless, if time permits, good nutritional status may be restored by tube feeding, particularly with defined formula diets. Short-term nutritional repletion of the moderately malnourished patient or nutritional maintenance of the previously healthy patient who cannot swallow is satisfactory through a nasogastric or nasoduodenal feeding tube or, in selected patients, an endoscopically placed percutaneous gastrostomy tube. Indwelling nasogastric tubes are unsatisfactory for long-term use because they often cause nasopharyngeal ulcerations and esophagogastric reflux around the tube. For patients whose gastrointestinal tract is unavailable for nutriment administration or who need rapid nutritional repletion so that antineoplastic therapy may begin quickly, the technique of TPN can allow cancer treatment to be administered.

ENTERAL NUTRITION

The simplest form of nutritional repletion would be a standard diet plus oral supplementation. However, in addition to mechanical obstruction of the gastrointestinal tract by the tumor, salivary gland function may be impaired and dulling of taste and olfactory function may occur. This makes oral nutrition less palatable, and the nutritional status of the patient may actually deteriorate despite attempts at oral feedings.

A great deal of emphasis has been placed on tube feeding and enteral access in the malnourished patient to deliver a known quantity and quality of nutrients. Access to the upper gastrointestinal tract can often be difficult owing to mechanical obstruction, discomfort from the indwelling tube, and occlusion of the feeding tube. The preferred route of enteral nutrition depends on the individual patient's condition as well as on the expertise of the oncologist and nutritional support team.

Routes of Administration

Nasogastric Tube Feedings

The nasogastric route is the quickest and simplest form of tube feeding, provided no mechanical obstruction is present. A 10F or 12F soft silicone elastomer (Silastic) tube can be inserted without need of fluoroscopic guidance in most cases. Placement of the tip of the catheter in the stomach, rather than the duodenum, usually suffices. The risk of aspiration can be minimized by gradually increasing the rate of tube feedings as well as elevating the head of the patient's bed. However, a patient with a poor gag reflex or weak oropharyngeal musculature may require placement of the tip of the catheter in the duodenum. The pylorus then acts as a valve to prevent regurgitation of small bowel contents back into the stomach. It is not uncommon for these patients to have disorders of gastrointestinal motility secondary to their inanition, necessitating a slow and gradual increase in the rate of feedings.

Many formulas for tube feeding are available. We prefer to use an isotonic formula because of its relatively low cost compared with hyperosmotic, elemental diets. However, patients may require specialized formulas depending on their medical problems, degree of protein-calorie malnutrition, and tolerance to feedings. Full-strength isotonic feedings are begun at 25 mL/h and gradually increased by 15 to 25 mL/h over 6 to 12 hours. Gradually, the feedings are advanced to the desired rate, which usually approximates 100 to 120 mL/h. Tolerance to this regimen is highly variable and depends on the patient's underlying medical condition, the time period

over which nutritional depletion occurred, the degree of cachexia, and the formula delivered.

Andrassy and coworkers[1] emphasized the importance of a normal serum albumin level in tolerating enteral nutrition. Several studies have noted that patients with normal serum albumin levels tolerate enteral feedings better than hypoalbuminemic patients.[1,14] However, a prospective, randomized study in adults has yet to confirm the efficacy of intravenous albumin supplementation for enhancement of tolerance of enteral feedings.

Should diarrhea occur, it may be necessary to switch the nutritional formula to a non–lactose-containing formula or to decrease the rate to a basal level and advance more slowly. Continued intolerance to advancing enteral feedings may necessitate cessation of enteral feedings and initiation of TPN.

Mechanical complications of nasogastric tube feedings are frequent and often cause tube feedings to be discontinued. Erosion of the nasal ala may occur secondary to a poorly positioned tube. Further, the tube can become clogged, requiring either replacement of the tube or vigorous flushing. We prefer to irrigate the feeding tube intermittently at least two to three times per day with plain tap water to ensure patency. Should occlusion occur in a well-placed tube, it may be necessary to obtain roentgenograms to ensure that a kink has not occurred. If no kink is present, then a solution composed of pancreatic enzyme capsules dissolved in water may be injected into the tube. After several hours, the enzyme solution may dissolve enough impacted formula to allow flushing of the tube. This procedure often enables the physician to salvage a well-placed feeding tube instead of having to replace it. A rare complication is development of tracheoesophageal fistula due to erosion of the tube into the trachea.

Esophagostomy Tube Feedings

An esophagostomy tube may be inserted with the patient under light general anesthesia or local anesthesia. Once placed, this tube's anatomic position provides greater comfort and cosmesis. Pharyngostomy tubes can also be placed through the pyriform sinus with the use of a local anesthetic. In patients with head and neck malignancies, esophagostomy tubes are of minimal use because the tube may violate an operative field.

Gastrostomy Tube Feedings

Gastrostomy tubes may be placed in patients who have unresectable head and neck malignancies or in those who will require prolonged preoperative and postoperative enteral nutritional support. Gastrostomy tubes were inserted before radiation therapy in a few patients who had lost substantial weight and in whom we anticipated that the radiation side effects would further compromise oral intake. These patients have literally breezed through their therapy compared with those with nasogastric feeding tubes. However, gastrostomy tube placement should be avoided in the patient who may later need the stomach as a conduit after pharyngectomy or esophagectomy. The gastrostomy tube is easily cared for by the patient or the family. Gastrostomy tubes allow bolus feedings as a convenience to the patient. The tube does not cross the lower esophageal sphincter, thus decreasing the risk of aspiration compared with nasogastric tubes.

Gastrostomy tube placement requires either a laparotomy or a percutaneous endoscopic gastrostomy. A standard Stamm or Janeway gastrostomy may be done in a relatively short time with the use of local, regional, or general anesthesia; however, this procedure is associated with significant risk in the malnourished patient. Complications may include bleeding, infection, separation from the abdominal wall with subsequent peritonitis, wound infection or dehiscence, and inadvertent removal of the gastrostomy tube. A tube dislodged within the first 24 to 48 hours postoperatively may require replacement in the operating room. Tubes dislodged later require immediate replacement since the gastrocutaneous tract may close in as short a time as 6 hours.

Percutaneous Endoscopic Gastrostomy

Percutaneous endoscopic gastrostomy was introduced in 1980. With the use of sedation and local anesthesia, a fiberoptic endoscope is used to place a gastrostomy tube.[27] Contraindications include upper gastrointestinal tract obstruction, coagulopathies, ongoing sepsis, and ascites. In addition, intervening colon between the stomach and the abdominal wall precludes safe placement. This procedure obviates the need for laparotomy and can be done with minimal morbidity. However, complications can occur, including peritonitis, gastrocolic fistula, peristomal leakage, dislodgement of the catheter, and infection around the catheter. Percutaneous endoscopic gastrostomy tubes are significantly smaller than those placed by laparotomy, but serial dilations can be done to allow placement of a larger tube once the stomach has become fixed to the underside of the abdominal wall. The rapid advancement of laparoscopic surgery has aided the percutaneous placement of gastrostomy tubes and has improved the safety of the procedure.

Jejunostomy Tube Feedings

A feeding jejunostomy tube may be indicated in the patient in need of enteral access who has had previous gastric surgery, in whom a gastric pull-through procedure is planned, or who has severe gastroesophageal reflux and cannot safely tolerate gastrostomy tube placement. These tubes require placement by laparotomy, although in some centers these tubes are placed percutaneously with radiographic guidance or by laparoscopy. For long-term feedings, a standard Witzel jejunostomy or Roux-en-Y (Maydl) jejunostomy is preferred. Needle catheter jejunostomies have enjoyed recent popularity, although occlusion becomes a problem with prolonged use. Also, dislodgement occurs commonly and replacement of the tube is nearly impossible. On the other hand, in a Witzel jejunostomy a larger-bore tube can be used and, if dislodgement is recognized early, replacement can be accomplished. However, proper replacement of any gastrointestinal access tube should be confirmed by roentgenographic study with injection of water-soluble contrast medium through the tube to ensure placement within the lumen of the bowel. A Roux-en-Y jejunostomy allows intermittent catheterization through a stoma.

A drawback of the use of jejunostomy tubes is that bolus feedings cannot be used. Continuous slow-drip infusions can be administered to avoid bloating and diarrhea. Cyclic feedings can be used to help maintain a somewhat normal life-style for the patient. Complications of jejunostomy placement include wound infection

and dehiscence. Bowel obstruction may rarely occur around the entrance site of the jejunostomy tube.

Choice of Formula for Enteral Nutrition

Commercially available formulas vary in their concentrations of protein, carbohydrate, and fat as well as other supplements such as fiber, electrolytes, vitamins, and trace minerals. In addition, the osmolality of these formulas varies from isotonic to hypertonic (approaching 1000 mOsm/kg H_2O). These enteral formulations are supplied as ready-to-use formulas or in a powder form to be reconstituted.

In general, the specific formulas can be categorized into elemental, polymeric, or specialized formulations (Table 11-1). Elemental diets derive their composition from short-chain peptides and amino acids, simple sugars, and medium-chain triglycerides. These diets are delivered to the gastrointestinal tract in their most elemental form and, therefore, require minimal digestive and absorptive capability. However, these diets are usually unpalatable and are often extremely hypertonic. We suggest using elemental diets in patients who have not used their gastrointestinal tract for a period of time and may be devoid of brush-border enzymes. However, these diets should be diluted at initiation of therapy to avoid problems with hypertonicity and subsequent gastrointestinal intolerance. Brush-border enzymes are inductive, and feeding substrate rapidly replenishes the corresponding enzyme; for example, feeding sucrose replenishes sucrase.[18]

Polymeric formulas usually have a lower osmolality than elemental diets and are often isotonic with serum. These formulas are more palatable and are composed of intact proteins, complex carbohydrates, and fats. They

TABLE 11-1. Commonly Used Commercial Enteral Formulas

	Calories (%)			Calorie Density	Protein	Fat	Carbohydrate	Osmolality
	Protein	Fat	Carbohydrate	(kcal/mL)	(g/L)	(g/L)	(g/L)	(mOsm/kg H_2O)
ELEMENTAL								
Criticare HN	14.0	4.5	81.5	1.06	38.0	5.0	220	650
Vivonex T.E.N.*	15.3	2.5	82.2	1.00	38.2	2.8	200	630
POLYMERIC								
Ensure	14.0	31.5	54.5	1.06	37.2	37.2	145	470
Ensure HN	16.7	30.1	53.2	1.06	44.4	35.5	141	470
Ensure Plus	14.7	32.0	53.3	1.50	55.0	53.3	200	690
Ensure Plus HN	16.7	30.0	53.3	1.50	62.6	50.0	200	650
Osmolite	14.0	31.4	54.6	1.06	37.2	38.5	145	300
Osmolite HN	16.7	30.0	53.3	1.06	44.4	36.8	141	300
Isocal	13.0	37.0	50.0	1.06	34	44	133	300
Isocal HCN	15.0	45.0	40.0	2.00	75	102	200	690
Isotein HN	23.0	25.0	52.0	1.20	67.8	33.9	156	300
Magnacal Liquid	14.0	36.0	50.0	2.00	70.0	80.0	250	590
Meritene Liquid	24.0	46.0	46.0	0.96	57.6	32.0	110	505
Resource Liquid	14.0	31.5	54.5	1.06	37.2	37.2	145	400
Sustacal	23.0	23.0	54.0	1.30	77.0	35	180	1000
Sustacal HC	16.0	34.0	50.0	1.50	61.0	58	190	700
SPECIALIZED PULMONARY FORMULA								
Pulmocare	16.7	55.2	28.1	1.50	62.6	92.1	106	520
FIBER-ENRICHED FORMULAS								
Enrich	14.5	30.5	55.0	1.10	39.7	37.2	162	480
Jevity Liquid	16.7	30.0	53.3	1.06	44.4	36.9	152	310
HEPATIC FORMULAS								
Hepatic-Aid II Instant Drink Powder	15	27.7	57.3	1.10	44	36	169	560
Travasorb Hepatic Diet	10.6	12	77.4	1.10	29.1	14	209	690
RENAL FORMULAS								
Amino Aid	4.0	21.2	75.0	2.00	19.0	47.1	366	1095
Travasorb Renal Diet	6.9	12	81.1	1.35	23.0	18.0	271	590

* Contains L-glutamine.

can be divided into lactose-free and milk-based diets. Formulas normally have a caloric density of about 1 kcal/mL, although increasing concentrations of fat can increase this caloric density to as much as 2 kcal/mL.

Specialized formulas may be used in patients with hepatic failure or renal failure. Patients with hepatic failure from chronic liver disease may benefit from a formula high in branched-chain amino acids and low in aromatic amino acids.[17] However, studies have shown that formulations containing high levels of branch-chain amino acids are no better than standard formulations in minimizing hepatic encephalopathy.[20] Patients with chronic renal failure may not tolerate high nitrogen loads and thus require specialized formulas high in essential amino acids and histidine.[2]

Nearly all standard formulas have a high-nitrogen companion product. These specialized formulas may be necessary in patients undergoing radical surgery with increased nitrogen requirements for anabolism. More recently, formulations have included fiber in an effort to provide bulk for stools and minimize diarrhea. Ongoing studies are presently evaluating the efficacy of fiber-containing formulas.

TOTAL PARENTERAL NUTRITION

Routes of Administration

Solutions for TPN generally contain 3.5% to 5% amino acids and 20% to 30% dextrose. The osmolarity of this solution is between 1800 and 2400 mOsm, necessitating infusion into a large-bore central vein rather than a peripheral vein. Most often, the subclavian vein is catheterized percutaneously by the infraclavicular approach so that the tip of the feeding catheter can be placed in the middle of the superior vena cava. Nutrients delivered through this catheter are diluted rapidly in the vena cava, resulting in less risk of inducing thrombophlebitis than if the infusion was into a smaller vessel such as the internal jugular vein. Accurate positioning of the catheter tip in the middle of the superior vena cava is verified by obtaining a chest roentgenogram before beginning infusion of the hypertonic TPN solution.

The TPN delivery system should not be used indiscriminately. Blood, blood by-products, and medication should be infused through an alternate vein, usually a peripheral vein, whenever possible. A simultaneous, peripheral intravenous infusion is often necessary to administer antibiotics, supplemental fluids, or chemotherapeutic agents. The incidence of catheter-related sepsis in our series of patients ranged from 1% to 6%; the highest rate of sepsis occurred in patients with head and neck cancers because they often had open wounds or tracheostomy stomas nearby that constantly contaminated the catheter dressing. Long Silastic catheters can be inserted into the middle of the superior vena cava through the antecubital vein. If these catheters are properly managed, TPN can be infused safely through them, thereby eliminating the problem of local dressing contamination.

Long-term venous catheterization of cancer patients can be accomplished with catheters permanently placed in the superior vena cava and tunneled on the chest wall to exit at a distance from any operative site in the neck region.[7,30] The attainment of venous access is becoming more difficult because sclerosing agents used to treat solid tumors eliminate peripheral veins. In fact, many oncologists are using central venous catheters for the initial administration of chemotherapy. This practice improves patient comfort and reduces troublesome thrombophlebitis. Many of these reports indicate that blood may be withdrawn and blood products administered through the permanently placed catheters and that the catheter may also be used for infusion of TPN. The reader should be cautioned that such reports come from medical units having physicians, nurses, and technicians highly skilled in the use of such catheters for multiple purposes. To generalize the use of central venous feeding catheters for multiple purposes in the head and neck cancer patient population would be disastrous because of the predictable increase in septic complications.

Catheter Care and Acute Effects of Total Parenteral Nutrition

The patient's catheter dressing and TPN delivery tube should be changed three times a week. The skin is prepared each time with a defattening agent and an antiseptic solution. An antimicrobial ointment and a sterile dressing are applied to cover the entrance site. When proper technique is always used, a single feeding catheter can remain in place for prolonged periods without complications.

The patient who develops a fever during TPN is presumed to have catheter-related sepsis unless another focus of infection is found. Diagnosis of catheter-related sepsis is confirmed by a blood culture and a catheter culture positive for the same organism. The catheter should be removed immediately, and the temperature usually returns to normal within 24 to 48 hours after catheter removal if the catheter was the source of infection. If a primary focus of infection other than the catheter is found and blood cultures are negative, the primary focus should be treated appropriately and the catheter left in place. A positive blood culture is an unequivocal indication for catheter removal. Twenty-four to 48 hours after the temperature has returned to normal and blood cultures have become negative, the feeding catheter can be reinserted into the superior vena cava, usually through the opposite subclavian or antecubital vein.

Exchanging catheters over a J-wire has become a popular technique. However, if the catheter tract is infected, introducing another catheter in the same tract does not alleviate the infectious complication. If the catheter is properly maintained, routine catheter changes should be unnecessary.

The patient who develops sudden cardiac failure or respiratory insufficiency during infusion of TPN should be evaluated for evidence of overhydration, myocardial infarction, or pulmonary embolus. Rarely, a catheter may erode through the wall of the vena cava or another smaller vein if the catheter is placed in an aberrant vein other than the vena cava.[12] Symptoms from catheter erosion may mimic heart failure, and a high index of suspicion is necessary to avoid a catastrophic outcome. Pleural fluid with a high glucose and triglyceride content confirms the diagnosis of catheter vascular erosion and requires evacuation of all pleural fluid by thoracentesis along with removal of the central venous catheter.

A constant rate of infusion of the hypertonic TPN solutions is necessary to promote proper utilization of the administered glucose, amino acids, minerals, and vita-

mins. Initially, 1000 mL is delivered in 24 hours to confirm the patient's ability to effectively metabolize the infused glucose. In the absence of glycosuria and hyperglycemia, the flow rate may be increased to 1000 mL every 12 hours. Pancreatic islet cells again need the opportunity to adapt with an increase in insulin output in response to the increased glucose infusion, but within the first 3 to 5 days the average adult usually tolerates a daily ration of 2500 mL of TPN. Extremely cachectic patients, however, may tolerate only 1500 mL/d until partial nutritional rehabilitation has been attained.

The abrupt cessation of TPN may lead to insulin shock or reactive hypoglycemia. For this reason, TPN should be tapered during a 24- to 48-hour period before completely discontinuing it. Certainly, before the administration of any general anesthetic, TPN should be tapered and discontinued the preceding 24 hours to prevent insulin hypoglycemia from going unrecognized while the patient is anesthetized and resulting in subsequent permanent brain damage.

Formulation of the Total Parenteral Nutrition Infusion Solution

The formulation of TPN for daily infusion into the patient with normal levels of sodium, chloride, potassium, magnesium, inorganic phosphorus, and calcium is given in Table 11-2. Administration of amino acids and hypertonic dextrose without the proper quantity of any one of these necessary elements significantly impairs the patient's ability to achieve positive nitrogen balance and tissue synthesis. The degrees of depletion of potassium, phosphorus, and magnesium often parallel the extent of protein-calorie malnutrition but are not necessarily reflected by their serum concentration in the cachectic patient. Not until adequate intravenous nutritional replacement of amino acid building blocks and energy stores has begun do the serum concentrations of these elements diminish and reflect more accurately the true magnitude of the total body deficit. As anabolism progresses and protein synthesis returns to normal, requirements for these elements are reduced. The reason for the increased need during anabolism in malnourished patients is unclear; however, potassium, phosphorus, calcium, and magnesium have a much higher concentration in the intracellular compartment than in the extracellular compartment, and loss of body mass probably results in a relative total body deficiency of these elements that is unmasked when lean tissue replenishment begins.

Generally, the patient can be expected to gain 2 to 4 kg during a 3-week interval of TPN; the initial 1- to 2-kg weight gain is rehydration, but then the patient should gain lean body mass at a rate of 0.25 kg/d. Body weight gain greater than 0.5 kg/d should be considered fluid retention, and the TPN delivery rate should be slowed or a diuretic administered.

If, during infusion of TPN, glycosuria is encountered in a patient with a continuously elevated blood glucose concentration, then the patient's capacity for metabolizing the administered glucose has been exceeded, and exogenous crystalline insulin may be supplied or the glucose delivery rate must be reduced. If this situation is encountered in a patient who is receiving inadequate calories, then insulin must be added to ensure adequate metabolism of the needed glucose. When additional insulin is necessary, we recommend it be added directly to the TPN solution rather than be given subcutaneously. We recognize that some of the crystalline insulin adheres to the bottle and the administration tubing; however, the amount of insulin lost in this manner is insignificant. If insulin is within the TPN bottle and the infusion stops, then insulin administration also stops. If insulin has been administered subcutaneously, however, and the infusion stops, marked hypoglycemia with its potential adverse clinical results might occur. The initial insulin dose should be 5 to 10 units/1000 mL, and the amount should be increased gradually until the blood glucose level returns to within 120 to 180 mg/dL.

Trace elements such as copper, manganese, iodine, chromium, and zinc are present in blood, plasma, and albumin and may be needed by cachectic patients before a major surgical procedure. They are not present, however, in the highly purified amino acid solutions. If a course of TPN is to last for more than 3 weeks, trace elements should be added to the nutritional solutions. Folic acid, vitamin K, and vitamin B_{12} should be administered on a routine basis or regularly as necessary.

Often, hypoalbuminemia must be treated early in the course of parenteral alimentation. Albumin given in doses of 12.5 to 50 g/d during the first few days of treatment should restore colloid osmotic pressure toward normal. In most patients, serum albumin concentration increases sufficiently within about 14 days of beginning TPN, and exogenous serum albumin is necessary for only a short time. Exogenous serum albumin is used only to increase colloid osmotic pressure when the patient's symptoms dictate that this is necessary; it is not used as a nutritional substance. Serum albumin is expensive, and its half-life is too long for it to be an efficient nutrient.

Ten percent intravenous fat solutions are isotonic, 290 mOsm/L, with a caloric density of about 1 kcal/mL and can be infused through a peripheral vein without fear of inducing thrombophlebitis. Linoleic acid, the essential fatty acid, is provided by the thrice-weekly administration of one 500-mL bottle of a fat solution. Animal research indicates that supplying 40% of the nonprotein calories as fat might be more beneficial to the cancer patient than supplying all nonprotein calories as glucose.[6] Similar observations are yet to be made in humans. There has been some fear that linoleic acid might be immunosuppressive when given intravenously.[29] However, careful evaluation of the immunologic effects of commercially available fat solutions has not shown immunosuppression in humans.[26] Therefore, 40% of calories can be safely supplied as fat emulsions, but with no practical advantages over using glucose as the primary energy source unless significant carbon dioxide retention

TABLE 11-2. Solutions for Total Parenteral Nutrition

500 mL 50% Glucose Plus 500 mL 8.5% to 10% Amino Acid Solution

Additives*

40–50 mEq sodium chloride
20–30 mEq potassium acetate
10–15 mEq potassium acid phosphate
10–15 mEq magnesium sulfate

* Multivitamins, trace elements, and calcium gluconate are added daily based on the available preparations.

is an anticipated problem. Because the respiratory quotient of fat is less than that of glucose, use of lipid as a calorie source results in less liberation of carbon dioxide than the oxidation of glucose.

RESULTS OF NUTRITIONAL THERAPY

Mullen and coworkers,[24] in 1979, developed a formula utilizing the relationships between the concentrations of serum albumin and transferrin with delayed cutaneous hypersensitivity and triceps skin fold thickness to develop a prognostic nutritional index (PNI). Mullen's group initially evaluated 161 surgical patients using the PNI and demonstrated an increasing incidence of morbidity and mortality with an increase in the PNI.[23] In a later study of 100 consecutive surgical patients with gastrointestinal cancers, these investigators confirmed the increase in surgical risk to the patient with a higher PNI.[5] Goodwin and Torres,[15] as well as Hooley and associates,[16] have adapted the PNI to patients with head and neck malignancies. These researchers confirm that the higher the PNI, the greater the likelihood of postoperative complications.

Not every patient treated aggressively with either TPN or enteral nutrition necessarily becomes replenished. Spanier and coworkers[33] correlated change in body composition with change in delayed cutaneous hypersensitivity reactions during TPN. Those patients who converted skin test reactions from negative to positive also had a significant increase in lean body tissue, thereby indicating a nutritional response to TPN. Those patients who failed to convert skin test reactions from negative to positive also failed to increase lean body mass in response to TPN. The induction of anabolism depends on the time, content, and method of administration of TPN solutions or enteral formulas, the degree of initial malnutrition, the initial and continuing catabolic response of the patient, the energy expenditure required during oncologic therapy, and the expertise of the physician in the technique of TPN. The delivery of the nutrient mixtures alone does not ensure nutritional repletion.

Preoperative Nutritional Therapy

As a rule, it is much easier to promote return of muscle strength, weight gain, significant rise in the secretory protein concentration, and improvement of immune function by preoperative nutritional repletion rather than by waiting until malnutrition has become a severe problem postoperatively. Müller and coworkers randomized patients with gastrointestinal tract cancer to 10 days of TPN preoperatively versus conventional fluid management.[25] Equal numbers of malnourished patients were in each group. The control group had significantly more deaths and major complications, particularly pneumonia and anastomotic breakdown. Skin test reactivity and retinol binding protein, prealbumin, and transferrin serum concentrations improved in the TPN group and declined in the control group. This randomized prospective study clearly demonstrates the value of preoperative nutritional repletion and maintenance in the surgery patient population. The length of time required to nutritionally replenish a patient preoperatively is controversial. Rickard and colleagues did sequential nutritional assessment while using TPN during the treatment of children with advanced neoplastic diseases.[28] Administering TPN for 9 to 14 days was often inadequate to result in a net increase in synthesis of either skeletal or visceral proteins, whereas 28 days of TPN did result in such anabolic changes. Our group has used TPN preoperatively to replenish malnourished patients with head and neck malignancies and, in a retrospective review of 70 patients, has found that an average of 16.1 days of TPN preoperatively was required to create a definable anabolic response in patients with severe malnutrition.[9] If time permits, aggressive enteral nutrition either orally, through nasogastric tubes, or through percutaneously placed gastrostomy tubes can be done. Unfortunately, the surgical oncologist does not always have the luxury of adequate time, and the intravenous route using TPN ensures an adequate caloric delivery without relying on absorption across a potentially malfunctioning gastrointestinal tract.

Flynn and Leightty[13] studied 36 patients who were considered malnourished before surgical treatment of their head and neck malignancies. Nineteen patients were randomized to receive enteral nutritional supplementation before surgery, whereas 17 patients were randomized to receive only nutritional counseling but no supplementations. Despite a bias toward a worse prognosis in the supplemented group, fewer complications occurred in this group, and there was a reduction in both postoperative morbidity and length of hospital stay compared with the unsupplemented group. Several randomized studies have compared parenteral nutrition with aggressive enteral nutrition, and most of these studies demonstrate no difference in rates of morbidity or mortality.[4,21] There is no question that enteral nutrition is less expensive, and every attempt should be made to manage malnourished surgical patients preoperatively in an ambulatory setting. To date, however, the studies comparing enteral versus parenteral nutrition have been done, for the most part, in nutritionally intact individuals. The efficacy of aggressive enteral nutrition versus parenteral nutrition and the rapidity of nutritional repletion of the malnourished surgical patient are difficult to evaluate. Therefore, when time is of the essence, our group relies on TPN.

Nutritional Therapy With Radiation Therapy and Chemotherapy

Daly and associates[10] studied the effects of optimal oral nutrition versus intensive nasogastric tube feedings during radiation therapy in 40 patients with squamous cell carcinoma of the nasopharynx and oropharynx. In this randomized study, the tube-fed group had a higher mean caloric and protein intake and less mean body weight loss than did the orally fed group. Nutritional parameters were improved in the tube-fed group, yet tumor response to radiation therapy, the duration of response to this treatment, and the length of survival was not significantly different between the two groups.

Malnutrition is a poor prognostic indicator for response to chemotherapy. Whether nutritional repletion, either by enteral or parenteral methods, can reverse malnutrition and convert a predictably poor responder to chemotherapy into a good responder remains unknown.

Unfortunately, many of the randomized, prospective trials reported to date do not compare response of the cancer to chemotherapeutic drugs with the host response to attempts at nutritional repletion.[8] In fact, host weight gain in these studies is often composed predominantly of an increase in total body water and fat mass with little increase in lean body tissue.

It is important to know if a previously malnourished patient who has been nutritionally replenished with TPN is a better candidate for response to chemotherapy or radiation therapy than is a malnourished patient. Overinterpretation of the available data and bias for or against the use of TPN in the cancer patient population have resulted in TPN's being withheld when needed or used when unwarranted. Review of available data indicates that TPN should be reserved for the truly malnourished cancer patients for whom there is available oncologic therapy. The malnourished patients for whom there is no available antineoplastic therapy have benefited little or not at all from the use of TPN, and the nutritionally intact patient gains weight primarily as water and fat and would be subjected unnecessarily to the inherent complications of TPN.

Use of Palliative Total Parenteral Nutrition

Total parenteral nutrition should seldom be used for treatment of the patient who has relapsed despite the use of all available methods of cancer therapy. Terminally ill patients may feel somewhat better during the TPN infusion, but this effect ceases rapidly once TPN is discontinued. The end result is prolongation of pain for the patient and anguish for the family. These patients should have every available opportunity to increase their enteral alimentation to establish a better sense of well-being.

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12

TIME–DOSE–VOLUME RELATIONS IN RADIATION THERAPY

JAMES T. PARSONS

Treatment planning is structured on the application of the basic radiobiologic parameters relative to the risk of infestation around the primary tumor and regional lymphatics and the probability of control with specific doses of irradiation. This approach has made radiotherapy an intellectually gratifying medical discipline.

Gilbert H. Fletcher[51]

A "standard fractionation" does not exist.

Rodney R. Million

The goal in treating cancer by irradiation is tumor control with a minimum of treatment complications. Various treatment schedules have evolved through the years in an effort to achieve this goal; whereas many schedules were developed through a rational stepwise progression of science and accumulated clinical experience, many others developed through a process of trial and error. It is now known that optimal control of cancer with a minimum of complications is best achieved by techniques that fractionate the radiation dose. There is no single method of dose fractionation that has been proved best, and there is not one that is right for all situations. In most radiation therapy departments, treatments are administered once daily, 5 days a week.

CONTROL OF TUMORS BY IRRADIATION

Sigmoid Dose–Response Curve

In its early years, radiation therapy was dominated by the concept of an all-or-none dose. Cancers and normal tissues were classified according to the number of threshold erythema doses that were necessary to produce cures or complications. In the 1930s and 1940s, Miescher, Holthusen, and Strandquist provided evidence that changed this concept; they produced sigmoid dose–response curves of the general form shown in Figure 12-1 for human skin cancer and normal tissue damage.[80,121,165] For homogeneous groups of tumors, such curves have now been shown for many sites other than the skin. These curves demonstrate the probabilistic nature of cancer control and normal tissue damage. For any given dose there is a corresponding tumor control probability and a corresponding complication probability. Tissue damage cannot be completely avoided since those doses expected to bring about cure overlap those that can cause complications. However, by manipulating the total dose, the total time over which the dose is administered, the fraction size, and the volume irradiated, an attempt is made to vary the relation between these two curves in a favorable way, that is, to improve the therapeutic ratio.

As shown in Figure 12-1, a small change in total dose would result in a large change in tumor control probability. In actual practice, tumor control probability curves are rarely so steep because not all of the cancers in the study population are homogeneous in their response to radiation. For example, if the cancers of half the patients analyzed are, for whatever reason, relatively resistant (ie, have a sigmoid response curve shifted to the right of the dose axis) and the other half are sensitive (response curve shifted to the left), the overall response curve is relatively flat even though the curves for each subgroup are steep.

Radiosensitivity and Radiocurability

After irradiation, cells die when they attempt to undergo division. A population of proliferative cells that has a

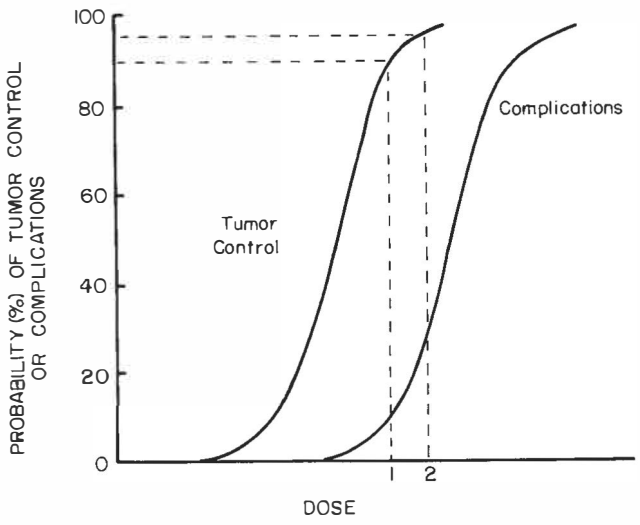

Figure 12-1. Dose–response curves for control of a hypothetical tumor and for normal tissue damage. Treatment to dose level 1 results in a 90% probability of cure and 10% probability of complications. Because of the shape of the sigmoid response curves, if the dose is increased to level 2, the control rate increases by only 5% but the rate of complications increases more dramatically to 28%. By manipulation of factors other than dose (such as time, fraction size, and treatment volume), the actual separation between the two curves may also be varied; for some treatment regimens or tumors types, the complication curve lies to the left of the control curve so that for any chosen dose, the complication rate exceeds the cure rate.

long cell cycle may be depleted slowly by irradiation, whereas the cells of a rapidly cycling tumor are more quickly eliminated. By the same token, a cell that never divides is not killed by irradiation, but it is not of consequence since it does not contribute to tumor growth.

The response of tumors to irradiation is commonly described in terms of radiosensitivity, radioresistance, and radiocurability. The terms *radiosensitivity* and *radioresistance* are imprecisely defined, loosely used, and a source of great confusion to clinicians. The term *radiosensitivity* is commonly applied to tumors that regress rapidly under treatment, whereas *radioresistant* refers to tumors that regress slowly. These definitions have an unfortunate connotation, since many clinicians have tended to equate slow regression with incurability. A *radioresistant* cancer, such as a slowly regressing adenocarcinoma of the prostate, might in fact be highly *radiocurable;* such lesions often show little or no size reduction at the completion of a 7-week course of therapy, but they gradually shrink and eventually disappear over a period of several months and then remain permanently controlled. Slow regression after irradiation has also been observed in some patients with slow-growing basal cell carcinomas (see Fig. 25-35).

For the first half of this century, radiosensitivity was thought to be a simple function of histology, with some histologic types (eg, squamous cell carcinoma) classified as radiosensitive and others (eg, adenocarcinoma) radioresistant. It is now believed that there is no essential difference in radiocurability of the various epithelial carcinomas of the head and neck. Squamous cell carcinoma, basal cell carcinoma, mucoepidermoid carcinoma, and adenocarcinoma are apparently, size for size, equally radiocurable.[49] A possible exception is lymphoepithelioma, for which control is achieved at lower doses than squamous cell carcinomas of equal size.[50] The probability of tumor control also does not depend in any clear way on tumor cell differentiation; although highly differentiated cancers may regress more slowly than poorly differentiated ones, ultimate control rates are similar.

Tumor cells have innate properties that determine their response to irradiation, the most important of which are susceptibility to damage and ability to repair that damage. Within the group of squamous cell carcinomas of the head and neck a wide range of radiosensitivities has been demonstrated using in vitro assay techniques that measure the survival at 200 cGy plus a number of other radiobiologic parameters that describe the shape of the cell survival curve. Preliminary data from Weichselbaum and Beckett,[191] Peters and associates,[143] and Fertil and Malaise[47] suggest that measuring radiosensitivity on biopsy material obtained before irradiation may someday be a useful parameter to help predict the probability of tumor control. Cellular radiosensitivity is but one of many factors influencing treatment outcome; it is unreasonable to expect that this parameter alone will provide sufficient information on which to base clinical decisions.

Soft tissue sarcomas have traditionally been regarded as incurable by irradiation. Many are locally advanced when detected and have a predictably poor control rate when treated with radiation alone; however, when used preoperatively or postoperatively, irradiation has been shown in many series to be an effective adjuvant to surgery, often enabling the surgeon to spare vital structures (nerve, blood vessels, bone) that would require removal if irradiation were not employed.[13,23,94,147,168] Small or moderate-sized sarcomas (less than 5 cm) in sites where the use of high-dose irradiation is feasible are sometimes cured by irradiation alone.[35,160,170]

Several benign histologies can be controlled with moderate doses of radiation. Chemodectomas of the temporal bone and juvenile angiofibromas are benign conditions for which irradiation is frequently chosen when the lesions are advanced or recurrent after surgery. Chemodectomas that have received more than 4000 cGy are almost all controlled if the treatment volume is adequate (see Chap. 30).[36] Giant cell tumors of the skull or jaw bone are occasionally treated with irradiation (4500 cGy) with high rates of success. Juvenile angiofibromas require even lower doses (3000 cGy). Benign mixed salivary tumors infrequently require irradiation since they are usually controlled by surgery alone; a small number of patients at the University of Florida have received high doses (6000 to 6500 cGy) for recurrent or residual disease. Results have been good (see Chap. 27).

Rate of Tumor Regression

For squamous cell carcinomas, it was common practice until the mid 1960s to base the total tumor dose on rate of regression during therapy.[12] As a result, some rapidly responding lesions were underdosed, leading to tumor recurrence. For the majority of squamous cell primary lesions, modification of total dose according to regression rate is probably not a good idea. Instead, at the outset of treatment, a dose is prescribed that is based on the initial volume of tumor; even if the lesion regresses rapidly, the full dose is administered. Most squamous cell primary carcinomas regress by at least 20% to

30% by 2 weeks, 50% to 60% by 4 weeks, and 80% to 100% by 6 weeks; completely exophytic lesions regress faster, and deeply infiltrative lesions regress slower. Metastatic lymph nodes regress slower than the primary lesion.[17] Although there are no specific data to prove the point, one cannot help but believe that at the extremes of responsiveness, ultimate control can be predicted by the regression rate.[14] It is rare to see recurrence of a squamous cell carcinoma that has completely disappeared 2 to 4 weeks into a 7-week course of therapy. On the other hand, lesions that show only 20% to 30% regression by 5 to 6 weeks are noted to recur with greater frequency. This is the basis for using a trial of irradiation for certain moderately advanced cancers. If the response at 5000 cGy has been good, a full course of irradiation is administered; if there has been only minimal regression, an operation is performed. Although assessment of clinical response at 5000 cGy would be an attractive parameter for predicting ultimate treatment outcome, there are few specific data that address the usefulness of this approach. Terhaard and coworkers[171] noted that in patients whose response was favorable (T-stage reduction or more than 50% tumor regression) at 5000 cGy, high rates of initial local control (ie, local control assessed 6 weeks after the completion of therapy) were obtained; the reported ultimate local control rates included salvage surgery so it was impossible to assess the control rates after irradiation alone.

At the Rotterdam Radiotherapy Institute, patients with T3–4 cancers of the supraglottic larynx were reevaluated after administration of 4000 cGy. If a good response was obtained, the treatment was continued to 6000 to 7000 cGy. Patients considered to have responded poorly were recommended to undergo operation. However, a number of patients whose tumors had responded poorly either refused or were medically unfit for laryngectomy and therefore also received radical irradiation. The 5-year local relapse-free survival rates were identical in the two groups after irradiation alone (47% for the good responders compared with 46% for the poor responders).[77]

The question of whether return of cord mobility after 5000 cGy is predictive of ultimate tumor control after high-dose irradiation has recently been addressed. Spaulding and coworkers[164] noted that the 3-year determinate local control rate in 22 patients with cancers of the supraglottic larynx and pyriform sinus whose vocal cords were initially fixed was significantly greater ($P = .04$) when mobility returned after administration of 5000 cGy. Parsons and associates[137] noted no difference in ultimate control according to cord mobility after administration of 5040 cGy (120 cGy twice a day) in patients with T3 vocal cord cancers. Control rates according to mobility at 5040 cGy were as follows: fixed, 4 of 5; partially mobile, 6 of 11; mobile, 2 of 3.

Aanesen and coworkers[1] irradiated 28 patients with T3 laryngeal carcinoma (20 glottic, 8 supraglottic) whose vocal cords were fixed before treatment. Patients whose vocal cords remained fixed after administration of 5000 cGy were advised to undergo total laryngectomy. Eight of 10 patients whose vocal cords remained fixed consented to laryngectomy, and in 4, no tumor was found in the surgical specimen. In the other two patients, all further treatment (beyond 5000 cGy) was refused; both patients remained free of tumor recurrence (at 2 and 7 years). Of 18 patients whose cord mobility returned to normal or near normal after 5000 cGy, 6 subsequently developed local recurrence. The authors concluded that return of mobility after treatment with 5000 cGy was of dubious prognostic value.

Although the correlation of tumor control with the rate of regression *during* therapy remains controversial, most observers agree that tumor status *at the completion* of treatment correlates with ultimate control. In an analysis of 1653 patients who received at least 5500 cGy external-beam irradiation (usually 6500 to 7500 cGy by shrinking fields at 200 to 220 cGy/d, 5 days per week) at the Institut Curie in Paris between 1958 and 1976, Bataini and coworkers[18] noted that the clinical appearance of the lesion proved to be an important parameter predictive of complete response. Lesions described as infiltrative or deeply ulcerative had a lower rate of complete regression than exophytic or superficial tumors ($P < .0001$). As expected, T1–2 lesions also regressed significantly more frequently than T3–4 tumors. Patients who had incomplete primary regression at the completion of treatment were generally at high risk of local failure.

Data on 146 patients with squamous cell carcinoma of the oral cavity, oropharynx, and hypopharynx after radical irradiation at the Strong Memorial Hospital[162] and on 125 patients with oropharyngeal cancers treated at the M.D. Anderson Hospital from 1966 through 1970[12] also showed significantly higher recurrence rates when there was clinical evidence of residual tumor on the last day of treatment than when complete regression had occurred. Bataini and associates[17] made the same observation with regard to metastatic neck nodes in 708 node-positive patients whose primary tumors were controlled by irradiation.

Significance of Positive Biopsy Findings After Irradiation

Even when cancer persists in the follow-up period, 1 to 3 months after treatment, lesions may continue to regress and be permanently controlled. Suit and Gallager[167] showed in animal tumors that the persistence of histologically intact tumor cells 3 to 6 weeks after irradiation did not indicate the probability of local recurrence, since such cells may be nonviable. The cells may still be capable of diverse metabolic activities, and some may even be able to divide a limited number of times before their progeny die; however, if their capacity for sustained proliferation is lost, they are biologically dead. Biopsy before 3 months after treatment is generally not recommended unless there is definite progression of cancer, which is a sure sign of treatment failure.

Tumor Size

The probability of tumor control depends on cancer size or, more precisely, on the number of clonogenic cells* present. Cell kill is exponential; that is, each increment of radiation kills the same proportion of cells, not the same absolute number of cells. Assume that 500 cGy is sufficient to reduce a malignant cell population by 90%. It takes the same dose of radiation to reduce the cell population from 10^8 to 10^7 cells (ie, to kill 90 million cells) as it does to reduce the population from 1000 to 100

* A clonogenic cell is one that is capable of regenerating a tumor, that is, of forming a clone.

cells, or 100 to 10 cells (ie, to kill 900 or 90 cells). Obviously, the larger the volume of cancer, the greater the required dose to achieve tumor control. Although this may not seem too difficult a concept, it is one that was disregarded by physicians for many years and continues to be ignored even today by some surgical, medical, and radiation oncologists. A debulking of 90%, or even 99%, of gross cancer by either preirradiation surgery or preirradiation chemotherapy may produce an impressive volume reduction but achieves little from a radiobiologic standpoint, since it reduces the tumor population by only one or two decades. In fact, a surgical debulking that leaves behind macroscopic disease probably lessens the chance of cure by irradiation. Several possible explanations exist:

1. When a cancer is cut across, tumor cells are disseminated throughout the surgical bed and may be implanted in relatively hypoxic scar tissue where they are less sensitive to irradiation.
2. Alternatively, the remaining cells may find themselves in an environment favorable to growth and begin to proliferate rapidly. The rapidity with which some recurrences are noted after surgery and irradiation in this situation fits well with this hypothesis.
3. Cancers that are depopulated by a dose of radiation often respond with a compensatory burst of accelerated proliferation. It seems likely that accelerated proliferation also occurs after grossly incomplete surgery.

The notion that different volumes of cancer require different doses is the basis for the shrinking-field concept of irradiation (Fig. 12-2). The initial treatment volume depends on the tumor size and its regional extensions; all gross and microscopic cancer must be included within the original field if control is to be achieved. After a certain dose, the fields may be reduced in size, since microscopic extensions require less total dose than gross cancer. That is, the dose is distributed in accordance with the number of cancer cells present.

Effect of Tissue Hypoxia

The ability of x-rays to kill cells is reduced under conditions of hypoxia. Since tumors tend to outgrow their blood supply, they contain hypoxic areas that may limit the success of radiation therapy.[176] The magnitude of the problem of hypoxia in clinical practice using fractionated therapy is not well known; even large, infected, ne-

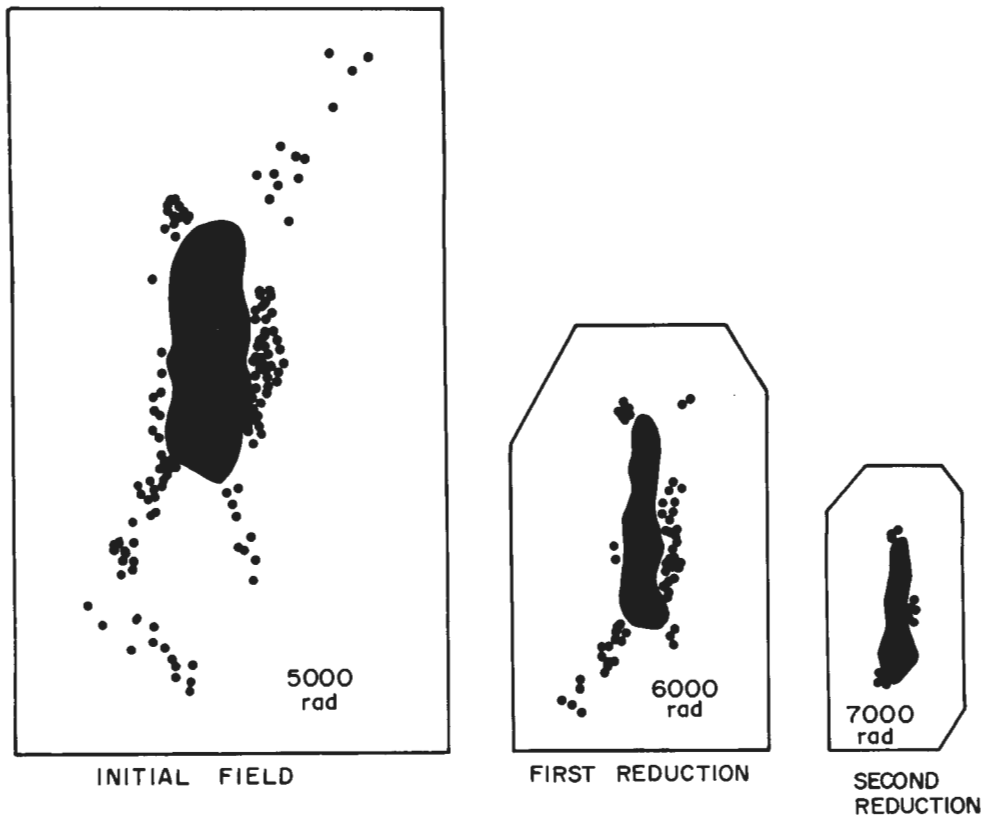

Figure 12-2. The shrinking-field concept of irradiation used in the treatment of gross cancer (*black area*) and its microscopic extensions (*dots*). The initial treatment volume covers all gross cancer and generously treats any suspected microscopic extensions. Because small volumes of cancer require less dose to achieve control than larger tumor volumes, the initial fields may be reduced, often at 5000 cGy, as in this hypothetical case. The area of moderate tumor infestation receives 6000 cGy, then a final reduction is made to boost the gross cancer to 7000 cGy or higher. The same concept of applying the greatest amount of treatment to the greatest bulk of cancer is used when combining irradiation and surgery, in which the operation serves as the "boost" treatment to the gross mass and the radiation sterilizes the peripheral tumor aggregates.

crotic tumors may be cured in substantial numbers, suggesting that the problem may be overcome by conventional therapy. During fractionated treatment of most animal tumors, the absolute number of hypoxic cells is not static. Reoxygenation occurs after successive doses.[71] A similar situation likely pertains in human tumors.

Anemia is potentially deleterious. Several observers have noted that anemic patients with squamous cell cancers of the larynx, pharynx, or uterine cervix have a decreased probability of cure after irradiation.[21,25,26,44,132,169] Whether this is secondary to an increased hypoxic cell fraction or is merely due to more advanced cancers in anemic patients remains controversial. In a multivariate analysis of Radiation Therapy Oncology Group (RTOG) protocol 79-15, in which irradiation alone was tested against irradiation plus misonidazole, the finding of low hemoglobin concentration was strongly associated with low Karnofsky performance score; hemoglobin concentration had no independent influence on local–regional control.[45] Several studies suggest that correction of anemia before treatment may improve local control.[26,33,44]

Tumor Site

During the first half of the 20th century, squamous cell cancer in lymph nodes was thought to be relatively resistant to the effects of irradiation compared with cancer at the site of origin. This observation was largely due to technical problems related to the manner in which kilovoltage x-rays could be applied. With more refined megavoltage techniques, this problem has been largely overcome. Small-volume neck disease is readily controlled with irradiation alone, whereas disease of larger volume is controllable with irradiation plus neck dissection.

There are differences in response of cancers to megavoltage irradiation according to the mucosal site of origin that are not explainable by our current knowledge. In some instances, cancers arising from sites only 1 or 2 cm distant from one another show markedly different responses. For example, squamous cell carcinomas of the oral tongue are less frequently cured by high-dose, megavoltage, external-beam irradiation alone than by combinations of external-beam plus implant or intraoral cone, or by implant or intraoral cone treatment alone. Either tumor repopulation or relative inherent radioresistance may be responsible for the poorer control rates that occur after less intensive regimens. Meanwhile, cancers of the base of tongue are readily controlled with external beam alone.[57] A similar observation applies to cancers of the tonsillar region: T1–2 cancers of the anterior pillar are significantly less frequently controlled than cancers of the tonsillar fossa when treated by conventional megavoltage techniques, again calling for different irradiation strategies for adjacent sites.[15,65,115,125,188] However, Mazeron and colleagues[109] reported that modest dose external-beam irradiation (4500 cGy) and higher dose interstitial irradiation (3000 cGy) produced local control in all of 15 T1–2 selected (superficial, minimally infiltrative, with minimal extension to the base of tongue or retromolar trigone) tonsillar pillar lesions. Peters has produced preliminary data showing that the intrinsic radiosensitivity (as measured by survival after 200 cGy) of oral cavity tumors may be significantly less than for oropharyngeal, hypopharyngeal, and laryngeal lesions, thereby justifying the need for more intensive strategies for the former tumors (Peters LJ, personal communication, April 1990).

Tumor Regeneration and the Effect of Overall Treatment Time

Most human tumors have a relatively slow growth rate, with volume doubling times on the order of 2 months. Tumor cell regeneration during a conventional course of fractionated treatment lasting 6 to 8 weeks has been, therefore, generally discounted as a cause of failure to achieve tumor control. There are now ample data to suggest that *after* a radiation injury, rapidly renewing normal tissues and some tumors recover by means of a regenerative response. Usually there is an acceleration of growth due to shortened cell cycle time and an increase in the proportion of cells that are actively proliferating (ie, growth fraction).[173]

There are fewer data documenting an accelerated rate of tumor regeneration *during* treatment,[91,196] as has been shown in some rapidly proliferating normal tissues.[126,196] Based on a review of many series of squamous cell carcinoma of the head and neck that show (1) dependence of TCD50 (the dose necessary to achieve local control in 50% of the cases) on overall treatment time, and (2) the relation between total dose, overall treatment time, and local control from published time–dose data, Withers and coworkers[197] have estimated that tumor clonogens in the average squamous cell carcinoma of the head and neck respond to treatment with a burst of rapid repopulation that commences 3 to 5 weeks after the start of radiation therapy. The dose increment necessary to compensate for this repopulation is consistent with a 4-day clonogen doubling rate, compared with a median of about 60 days noted in published reports of unperturbed tumor growth rates. The latter type of unperturbed repopulation (ie, assuming no accelerated growth of tumor clonogens) would have little measurable effect on the likelihood of tumor control, because the dose increment required to balance this type of tumor growth (assuming a 6- to 8-week treatment course) is estimated to be only 200 to 300 cGy. The former type of repopulation, accelerated repopulation, is believed to be a major determinant of tumor control probability.

If it is reasonable to assume that acceleration of tumor growth occurs during fractionated treatment of human squamous cell carcinomas, then once treatment is begun, it should be completed in as short a time as is consistent with an acceptable level of acute toxicity, preferably without reducing the total dose. Historically, the aim of prolonging the overall treatment time was to minimize acute toxicity. Excessively protracted treatment schemes, such as the split-course approach used at the University of Florida (see below), appear to be clinically disadvantageous, probably because of accelerated repopulation of clonogenic cells during and after the rest interval. Data on cancers of the oral cavity and oropharynx suggest that the probability of local control correlates with the severity of acute response, suggesting that attempts to minimize acute toxicity by treatment protraction may reduce the chances of tumor control.[99]

It is important to recognize that accelerated regrowth of tumors is *not* detectable clinically during the course of treatment. In fact, the observed tumor response may ap-

pear gratifying, with total or near-total regression of clinically apparent cancer by the time a split in treatment is introduced and continued regression of gross disease during a split. However, one should not be lulled into complacency by this gross response, because the tumor cells that remain may be regrowing at a markedly accelerated rate, thereby seriously limiting our ability to achieve ultimate control. This seeming paradox (rapid regrowth of surviving clonogens during a time of continued regression of the largely sterilized tumor mass) was shown to occur in animal tumors more than 20 years ago, but its importance in human tumors was not recognized until much later.[76]

Host Factors

Other important factors that influence the rate of local–regional tumor control include the gender[132] and performance status of the patient. In a number of series, local control rates in female patients with vocal cord cancer were significantly higher than in male patients.

Elective Irradiation of Subclinical Disease in the Neck

The term *subclinical cancer* refers to tumor deposits that are too small to be detected clinically, despite being present in sites accessible to examination. The terms *microscopic disease* and *micrometastases* are often incorrectly used as synonyms for subclinical disease. Subclinical deposits are not always microscopic; in some circumstances, the tumor may remain subclinical despite being *macroscopic*, that is, several millimeters or even a centimeter in size. The existence of subclinical lymph node metastasis has been well documented by the observations that many patients with clinically negative necks (1) are found to have histologically positive neck specimens if an elective neck dissection is performed or (2) develop regional nodal recurrence despite control of the primary lesion if no neck treatment is administered. For most head and neck sites, the incidence is at least 20% and may be as high as 60% to 70% in certain situations (see Table 6-2). The dose prescribed for elective neck irradiation usually has been 4500 to 5000 cGy, but the maximum dose to high-risk first-echelon lymph nodes in the upper neck often exceeded 6000 cGy because these lymph nodes were within the primary portals. Of 162 patients who received partial or total elective neck irradiation and whose primary tumors (of the oral cavity, oropharynx, hypopharynx, supraglottic larynx, or nasopharynx) were controlled, 2 patients (1.2%) developed in-field nodal recurrences (one at the primary field margin and one in the low neck after administration of 4050 cGy in 15 fractions).[111]

In 1975, a new protocol for treatment of the low neck was initiated, delivering 4050-cGy dose given (at Dmax) in 15 fractions (5 fractions per week) through an en face low neck portal. The standard dose for elective irradiation of the low neck before 1975 was 4700 (5000 roentgen [R]) to 5000 cGy in 25 fractions. After 1975, 4050 or 5000 cGy was given at the discretion of the attending physician. Mendenhall and coworkers[117] compared the rates of nodal recurrence between the two treatments in four risk groups (based on the estimated likelihood of subclinical disease in the neck). There was no difference in the rate of neck disease control for the two dose–fractionation protocols. One failure (1%) developed in the low neck in 83 patients whose low necks were initially negative and who received 4050 cGy. No failure developed in 79 patients who received 5000 cGy to the low neck. In the group of patients at highest risk (those with clinically positive upper neck nodes), none of 23 patients who received 4050 cGy in 15 fractions and none of 30 who received 5000 cGy in 25 fractions had treatment failure in the low neck.

Control of subclinical disease by irradiation is not an all-or-none phenomenon. As in the case of gross cancer, a sigmoid dose–response relation is apparent for subclinical disease. After low-dose preoperative irradiation (3000 cGy midplane at 200 cGy/d, usually from a single ipsilateral portal) for squamous cell carcinoma of the pyriform sinus, Marks and coworkers[105] noted a substantial number of failures in the contralateral, initially clinically negative neck that had received a low dose of radiation. Similar results were noted by Perez and associates in the treatment of tonsillar fossa lesions with preoperative irradiation.[141] Of 77 patients with T1–4, N0–2 disease who received 3000 cGy over 3 weeks by way of an ipsilateral portal followed by an en bloc radical tonsillectomy and ipsilateral neck dissection, 7 patients (9%) developed failures in the contralateral neck. The estimated dose to the contralateral neck was 1800 cGy. In 69 similarly staged patients treated by irradiation alone, the contralateral neck received about 5000 cGy and no neck failures were observed. The relation between probability of control of subclinical metastasis and dose is shown in Table 12-1 for patients with clinically negative, surgically undissected necks.[48,82,112] About 70% of subclinical deposits are controlled by 3000 to 4000 cGy; higher doses control a greater proportion. There is a plateau at about 5000 cGy, a dose at which failures are exceptional and usually related to geographic miss.[20,48,56,122]

Irradiation for Control of Gross Cancer

The sigmoid dose–response curve means that a certain dose of radiation has a certain probability of controlling a lesion of a given size. For example, 2-cm neck nodes are controlled about 50% of the time by 5000 cGy.[50] Since the shape of the sigmoid curve is steep in its midportion, an increment of only 1500 cGy is capable of increasing the control rate of such nodes to about 90%. Further increases to 7000 cGy or even 8000 cGy do not control 100% of the cancers because the plateau portion of the curve has been reached. Attempts to achieve 100% control by using extremely high doses are futile and result in unacceptably high complication rates.

Tumor Recurrence Times

Between September 1964 and August 1976, 468 patients with previously untreated squamous cell carcinoma of the oral cavity, oropharynx, nasopharynx, supraglottic larynx, or hypopharynx were treated with curative intent at the University of Florida by external-beam irradiation alone or by external-beam irradiation plus an interstitial radium boost. One hundred sixty-one patients developed in-field primary recurrences after treatment; 155 (96%) of the local recurrences occurred within 24 months after treatment. The greater the tumor volume, the shorter was the median time to recurrence

TABLE 12-1. Efficiency of Elective Neck Irradiation (ENI) for Subclinical Disease by Dose of Irradiation

Author	Tumor Site	Patients	Dose to Neck	Percentage of Patients With N0 → N+ Conversion Following Treatment		Efficiency*
				No ENI	ENI	
Fletcher[48]	Oral cavity with N1–2 ipsilateral neck disease	99	3000–4000 cGy over 3–4 wk to contralateral neck	35%†	10%†	71%
Horiuchi and Adachi[82]	Oral tongue	37	4000 cGy over 3½–4 wk	37%	5%	86%
Mendenhall and coworkers[112]	Oral cavity	40	4500–5000 cGy over 5 wk	26%	0‡	100%
Fletcher[48]	Faucial arch with N1–2 ipsilateral neck disease	82	5000 cGy over 5 wk to contralateral neck	30%†	0†	100%

* Efficiency (%) = (1.00 − [failure rate following ENI/failure rate without ENI]) × 100%.
† Failure rate in contralateral N0 neck.
‡ Excludes one out-of-field failure.

(9 months for T1–2 and 4½ months for T3–4 lesions). By 24 months, the cumulative recurrence curve for all stages asymptotically approaches 100%. Two years is therefore an adequate interval of time to assess local control in squamous cell carcinomas of head and neck sites with the possible exception of the true vocal cord. True glottic lesions tend to recur later than squamous cell carcinomas at other head and neck sites. Fletcher and coworkers,[55] in analyzing 65 recurrent T1–2 glottic cancers, noted that by 3 years only 74% of the recurrences had appeared; by 7 years 94% of the recurrences were observed, but even at 10 years occasional patients continued to experience failure. In the University of Florida experience,[118] 83% of recurrences had occurred by 2 years, 93% by 3 years, and 98% by 5 years. Late failures have been classified as local recurrences, regardless of when they occurred; it is probable that in some instances they were really new primary lesions.

Two years is inadequate follow-up for some histologies, especially adenoid cystic carcinoma. All five patients with adenoid cystic carcinoma of the nasal cavity and ethmoid/sphenoid sinuses treated by radical irradiation alone at the University of Florida between 1964 and 1983 developed late recurrences (3½, 4, 5, 5, and 12½ years after treatment).[136]

TIME–DOSE (ISOEFFECT) DATA FOR SQUAMOUS CELL CARCINOMA OF VARIOUS HEAD AND NECK SITES

Dose Specification

It is generally possible to encompass the area of gross disease within the 93%- to 98%-of-maximum isodose line. There is considerable variation from institution to institution in the methods of dose specification.

When the treatment time is prolonged, the total dose must be increased to produce the same effect. A popular means of presenting complex clinical time–dose relations is with isoeffect curves or lines. For each tumor (patient) within a homogeneous group of cancers, one displays on a two-dimensional graph the tumor dose in centigrays (ordinate) versus the overall treatment time in days or number of fractions in which the treatment was given (abscissa); a log-log scale is generally used. If treatment is administered 5 days per week, then the total treatment time is closely related to the number of fractions. For some fractionation schemes, however, there is little correlation between the fraction number and the overall treatment time. When trying to demonstrate a time–dose relation, it is essential that lesions be grouped according to tumor volume, since larger tumors require progressively higher doses. Generally, separate analyses are performed for each T stage.

Equal tumor effect may be obtained by a variety of combinations of total dose and overall treatment time, and the line that connects these points of equal effect on the graph is the isoeffect, or equal effect, line. Theoretically, one can draw lines that describe treatment schedules likely to yield control rates ranging anywhere from 0% to over 90%. Effects other than tumor control (eg, acute normal tissue reactions or late complications) can also be expressed on these time–dose plots; the curves that describe these effects may or may not be parallel to each other or to the tumor effect curves. A treatment plan is generally chosen by weighing the probability of tumor control against the probability of producing a serious complication.

Time–dose data are available for a number of tumor systems and are helpful in the formulation of treatment plans. It is important to recognize that the data are generally available over rather narrow ranges of time and dose; extrapolation of the isoeffect lines beyond the zones for which there are available clinical data is unjustified and unsafe (see later). In the time–dose scatter distributions that follow, patients whose tumors recurred because part of the tumor was not within the treatment volume (geographic miss) have been excluded, since treatment of these patients would fail no matter what the dose.

Supraglottic Larynx

University of Florida time–dose data for T2–3 lesions of the supraglottic larynx are shown in Figure 12-3. In the range of doses employed, local control was achieved in 12 of 13 patients (92%) whose treatments were given at greater than or equal to 900 cGy per week compared with 9 of 15 patients (60%) whose treatments were administered in longer overall treatment times.

Issa[85] reported the results of an aggressive treatment schedule (6600 to 7400 cGy over 5½ to 7 weeks, five fractions per week, 220 to 240 cGy per fraction) for cancer of the supraglottic larynx. Local control was obtained in a high percentage of patients (T1–2, 30 of 30 [100%]; T3, 18 of 22 [82%]; and in 14 of 16 patients [87%] whose vocal cords were fixed), but the overall rate of severe late complications was high (14% overall and 20% of patients whose primary tumors were controlled).

Glottic Larynx

Stage T1–2

UNIVERSITY OF FLORIDA DATA. Mendenhall and coworkers analyzed the results of radical irradiation in 304 patients with previously untreated T1–2 squamous cell carcinoma of the vocal cord who received treatment at the University of Florida between 1964 and 1984.[118] Patients were treated with a continuous course, 5 days per week. All patients had a minimum 2-year follow-up, and 82% had at least 5 years of follow-up. Patients were excluded from analysis of local control if they died within 2 years of treatment with the primary site continuously disease-free. Patients were grouped according to tumor extent and according to the minimum type of operation that they would have required (had they been treated surgically).

Patients in the group suitable for treatment by cordectomy (T1A) had tumor confined to one vocal cord with or without anterior commissure involvement. Patients were further subdivided according to lesion length (less than 5 mm, 5 to 15 mm, more than 15 mm). Local control was achieved in all 12 patients in the cordectomy group who had T1A lesions less than 5 mm in length.

Local control results in 78 patients in the cordectomy group with T1A lesions 5 to 15 mm in length are shown in Figure 12-4*A*. The local control rate was 73 of 78 (94%). The data are summarized in Table 18-5 in Chapter 18 and show a higher rate of control for patients who received 6100 to 6500 cGy at 225 cGy per fraction compared with patients treated at the same rate but to lower total doses or compared with patients who received 6100 to 6700 cGy in a greater overall treatment time (ie, with a lower dose per fraction).

Local control results for 50 patients in the cordectomy group with T1A lesions greater than 15 mm in length are shown in Figure 12-4*B*. Local control was achieved in 45 of 50 patients (90%). Forty-one of 44 patients (93%) who received 6100 to 6500 cGy at more than 215 cGy per fraction experienced local control of their tumors versus only 1 of 3 patients treated to the same total doses at slower rates.

Stage T1B lesions involved both vocal cords. Of 15 patients who would have been suitable for treatment by hemilaryngectomy, control was achieved in 14 (93%) versus 15 (94%) of 16 patients who would have required total laryngectomy. The results are shown in Figure 12-4*C*. Although no time–dose response is noted, this may be due to insufficient data (ie, only two failures).

Stage T2A lesions were those in which vocal cord mobility was normal. Of 27 patients who met the classic criteria for hemilaryngectomy, 23 patients (85%) experienced local control after irradiation. The data for this group are shown in Figure 12-4*D* and summarized in Table 18-5 in Chapter 18. Local control was obtained in 15 (94%) of 16 patients who received 6100 to 6500 cGy at 225 cGy per fraction versus 7 (70%) of 10 patients who received 6100 to 7000 cGy at 180 to 220 cGy/d.

In patients with T2A lesions who would have required total laryngectomy, local control after irradiation was achieved in 27 of 38 patients (71%). Results are shown in Figure 12-4*E* and are summarized in Table 18-5 in Chapter 18. Local control was achieved in 17 of 18 patients (94%) who received 6100 to 6500 cGy at 225 cGy per fraction versus 4 of 11 (36%) who received 6100 to 7000 cGy at 180 to 220 cGy per fraction.

For patients with T2B lesions, the control rate after irradiation in patients who could have been treated by hemilaryngectomy (13 of 18, or 72%) was the same as for those who would have required total laryngectomy (18 of 25, or 72%). The results for both T2B groups are therefore combined in Figure 12-4*F* and are summarized in Table 18-5 in Chapter 18. There is a trend toward higher con-

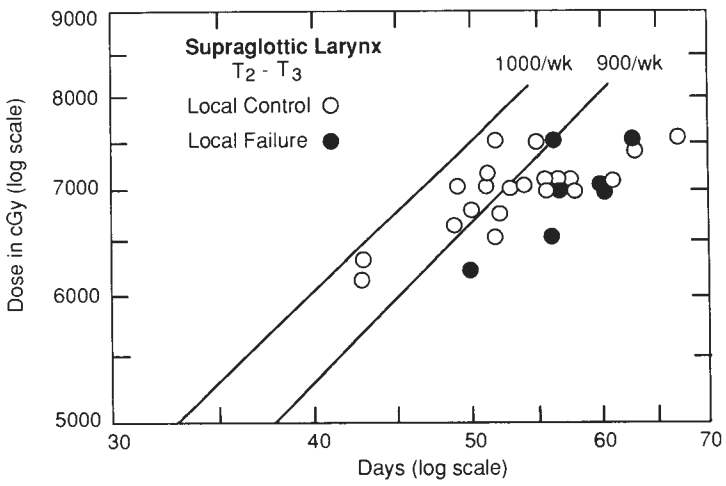

Figure 12-3. Time–dose scatter distribution for T2–3 squamous cell carcinoma of the supraglottic larynx treated with continuous-course once-a-day irradiation at the University of Florida from October 1964 to May 1981. The time axis represents overall treatment time in days. Reference lines, representing treatments administered at 1000 and 900 cGy/wk, respectively, have been added for reference purposes only; they are not intended to represent isoeffect lines.

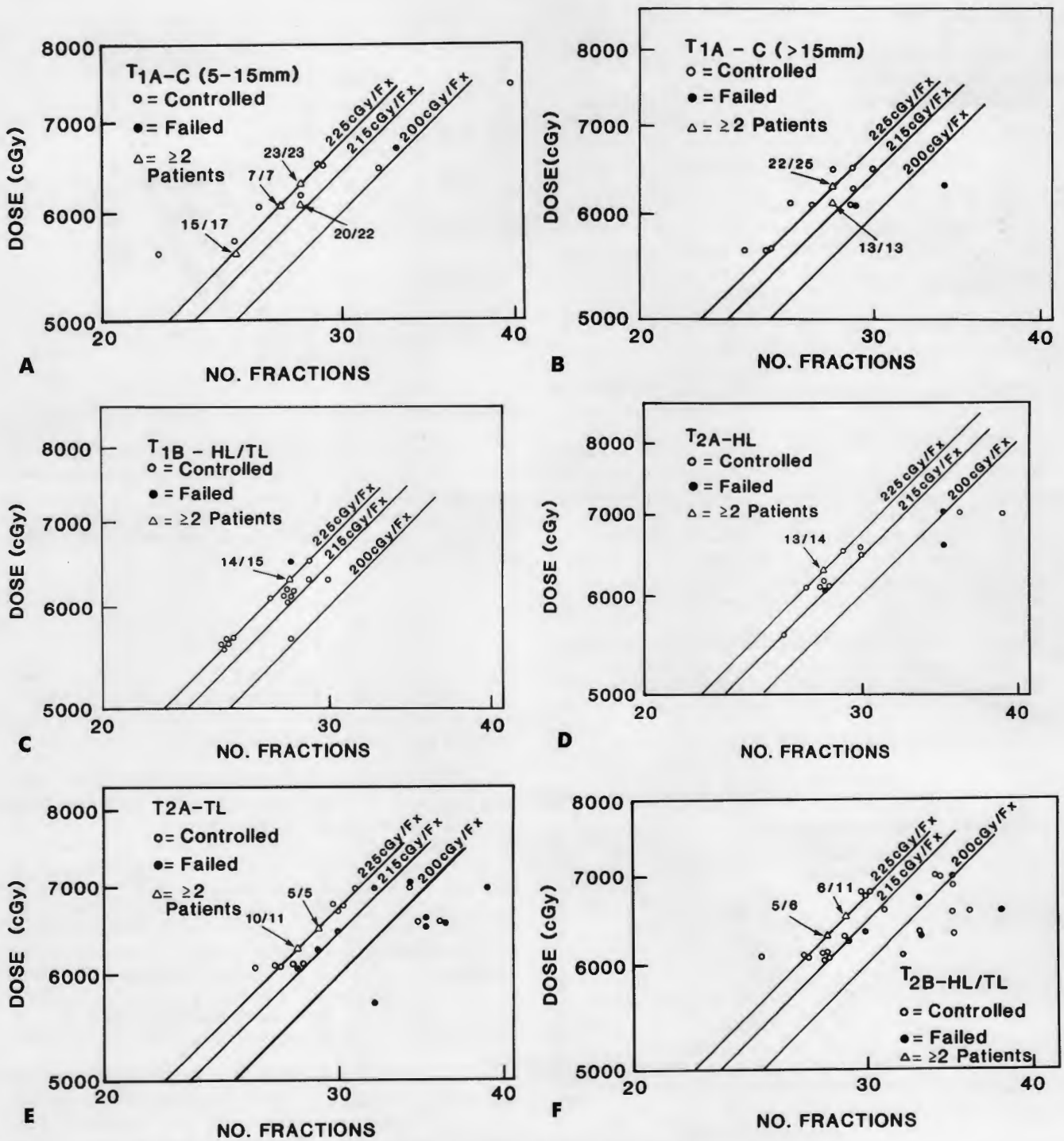

Figure 12-4. Local control of T1–2 carcinoma of the glottic larynx treated with radiation therapy alone as a function of dose and number of treatment fractions. The lines are not isoeffect lines and are for reference only. A circle indicates a single patient; a triangle denotes two or more patients. The number of patients represented by each triangle is given (number with disease locally controlled over the number treated, with arrow pointing to triangle). (*A*) T1a–C (5 to 15 mm). (*B*) T1a–C (larger than 15 mm). (*C*) T1b–HL/TL. (*D*) T2a–HL. (*E*) T2a–TL. (*F*) T2b–HL/TL. C, suitable for cordectomy; HL, suitable for hemilaryngectomy; TL, suitable only for total laryngectomy; HL/TL, patients suitable for a hemilaryngectomy plus patients suitable only for a total laryngectomy. (Mendenhall WM, Parsons JT, Million RR, Fletcher GH. T1–2 squamous cell carcinoma of the glottic larynx treated with radiation therapy: relationship of dose–fractionation factors to local control and complications. Int J Radiat Oncol Biol Phys 1988;15:1270)

trol rates in patients who received 6100 to 6800 cGy at 200 to 225 cGy per fraction (19 of 25, or 76%) versus those who received the same or slightly higher total doses in longer overall times (11 of 17, or 65%).

The incidence of moderately severe and severe complications according to tumor dose and number of treatment fractions is shown in Figure 12-5. For patients who received 6000 to 6500 cGy at 215 to 225 cGy per fraction, the risk of complications was 3 of 213 (1.4%). Two of 7 patients with advanced T2 lesions who received 6750 to 6975 cGy at 225 cGy per fraction developed complications. The latter dose schedules have been discontinued. Since 1986, patients with T2 vocal cord cancer have received 7440 cGy in 62 fractions (120 cGy twice a day).

OTHER DATA. Although it is standard practice in some institutions to use 6×6-cm fields for T1 vocal cord cancer, there would seem to be little reason to do so. In a trial involving 87 patients with T1N0 glottic carcinoma, Teshima and coworkers[172] randomly assigned patients to receive treatment through either 5×5-cm portals or 6×6-cm portals. All patients received 6000 cGy over 6 weeks with 4-MV x-rays. The 3-year local control rates were the same (93% compared with 96%), whereas both the acute mucosal reaction ($P < .05$) and persistent (more than 6 months) arytenoid edema ($P < .02$) were significantly more severe in the 6×6-cm group. Although a change from 5×5 cm to 6×6 cm may sound trivial, it results in a substantial increase in the volume of tissues receiving high-dose irradiation.

The University of Florida data on time–dose relations for control of early vocal cord cancer are confirmed by other reports. Schwaibold and associates[156] noted local failure in 7 of 28 patients (25%) with T1 vocal cord cancer after administration of 6600 cGy at 180 cGy per fraction versus 0 of 28 who received similar doses at greater than or equal to 200 cGy per fraction ($P = .01$). In a separate analysis that included a time–dose scattergram of these data, it was noted that local control was achieved in all 24 patients whose overall treatment time was less than 51 days versus 25 of 32 patients (78%) whose treatments lasted 51 days or more, despite the fact that the latter group generally received higher doses.[157]

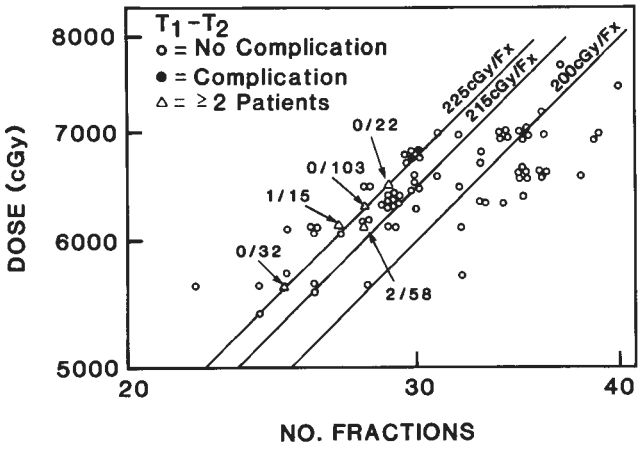

Figure 12-5. T1–2 carcinoma of the glottic larynx treated with radiation therapy alone. Incidence of moderately severe and severe complications as a function of dose and number of treatment fractions. The lines are not isoeffect lines and are for reference only. A circle indicates a single patient; a triangle denotes two or more patients. The number of patients represented by each triangle is given (number sustaining a moderately severe complication over the number treated, with arrow pointing to triangle). (Mendenhall WM, Parsons JT, Million RR, Fletcher GH. T1–T2 squamous cell carcinoma of the glottic larynx treated with radiation therapy: relationship of dose–fractionation factors to local control and complications. Int J Radiat Oncol Biol Phys 1988;15:1271)

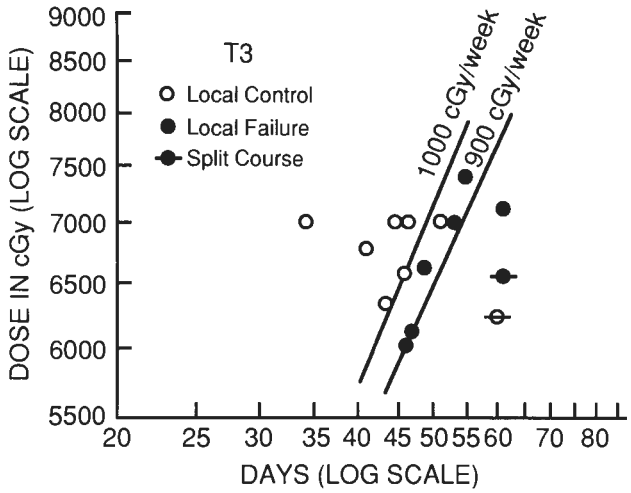

Figure 12-6. T3 vocal cord cancer treated with once-a-day fractionation at the University of Florida. The lines represent treatments administered at 1000 and 900 cGy/wk, respectively, and are for reference only. They are not isoeffect lines. (Modified from Mendenhall WM, Million RR, Sharkey DE, Cassisi NJ. Stage T3 squamous cell carcinoma of the glottic larynx treated with surgery and/or radiation therapy. Int J Radiol Oncol Biol Phys 1984;10:359)

Kok[89] treated stage I larynx cancer to 6300 cGy, 5 fractions per week, in daily fractions of 175 cGy (for 36 fractions), 190 cGy (for 33 fractions), or 210 cGy (for 30 fractions). The regimen using 175 cGy per fraction was quickly abandoned after local control was noted in only 1 of 3 patients. The control rate in the patients given 190 cGy per fraction was 12 of 14 (86%) versus 4 of 4 (100%) in the group given 210 cGy/d. Kok concluded that "a difference in fraction-dose of only 10% can be decisive."[89]

At the University of California, San Francisco, in the late 1950s, emphasis was placed on low daily doses for early vocal cord cancer to avoid acute mucosal reactions.[24,181] In general, 180 cGy per fraction was used to administer total doses of 5500 to 7000 cGy,[199] but in many cases the daily dose was closer to 160 cGy.[24] With these protracted schedules, the local failure rates were 20% for T1 and 48% for T2 lesions, twice those usually reported.

Stage T3

For T3 vocal cord cancer, Harwood and coworkers[75] showed a clear dose–response relation. The University of Florida data for a small number of patients treated with once-a-day fractionation are shown in Figure 12-6 and also suggest the importance of time–dose factors.[113]

TABLE 12-2. Local Control After Megavoltage Irradiation of Early Oropharyngeal Carcinomas Receiving 5500 to 6500 cGy Over Less Than 5 Weeks*

T Stage	Glossotonsillar Sulcus[159] (1954–1972)	Base of Tongue[163] (1954–1971)	Tonsillar Fossa[158] (1954–1968)	Anterior Tonsillar Pillar/Retromolar Trigone[11] (1954–1973)	Soft Palate[65] (1954–1967)	Total, All Sites
T1		5/6	5/5		18/18	28/29 (97%)
T2		2/3	4/4		30/30	36/37 (97%)
T3		4/4				4/4 (100%)
T2–3	3/3					3/3 (100%)
T1–3				28/30		28/30 (93%)

* No time–dose scatter distribution for soft palate lesions has been published. Patients generally received 5500 to 6000 cGy over 4 to 5 weeks.[50]
Note: M. D. Anderson Hospital data.

Oropharynx

In the treatment of oropharyngeal cancers in the early megavoltage years at M.D. Anderson Hospital, the generally recommended plan was 6000 cGy over 4 weeks when field sizes were less than 50 cm^2, 6000 cGy over 5 weeks when 50- to 80-cm^2 portals were used, and 6000 cGy over 6 weeks plus a boost when portals were over 80 cm^2.[163] As the irradiation technique evolved through the years, larger treatment portals were used, because there were some marginal recurrences with the small fields and more generous coverage of the subdigastric nodes was desired. The use of larger fields often meant that the 4- or 5-week treatment schemes were not practical because of marked acute reactions and late fibrosis, but even so, published time–dose data indicate that many T3–4 lesions received, on average, more than 1000 cGy over 1 week, either by the use of high doses per fraction throughout the treatment course or by the use of 200 cGy per fraction until the final boost, after which the dose per fraction was increased.

Treatment results at the M.D. Anderson Hospital (1954 to 1973) in patients who received 5500 to 6500 cGy over less than 5 weeks for early carcinomas of the oropharynx were extracted from time–dose scattergrams (Table 12-2).[11,65,158,159,163] The patients in Table 12-2 had mostly early lesions, and often the smallest lesions within a stage were chosen for short treatment courses.[163] Notwithstanding this fact, the control results (99 of 103, or 96%) are exceptional.

Very high rates of control were also achieved in patients with T3–4 cancers of the tonsillar fossa who received 6500 cGy or more and those with base of tongue cancers who received 7000 cGy or more at average weekly dose rates of 1000 cGy or more (Table 12-3). The use of large daily fractions is a double-edged sword, and one must balance the higher control rate against acute reactions and late complications, which are also more severe.

Tonsillar Region

The University of Florida's time–dose data for T1–2 squamous cell carcinoma of the tonsillar fossa treated with continuous-course once-a-day irradiation are shown in Figure 12-7*A*.[115] No local failures were observed.

Time–dose data for T1–2 squamous cell carcinoma of the anterior tonsillar pillar are shown in Figure 12-7*B*.[115] No clear time–dose relation is apparent. Control results are worse in patients with anterior pillar lesions than fossa lesions (Table 12-4).[15,65,125,188] For pillar lesions, attempts should be made to shorten the treatment time, either by using an intraoral cone before external beam or by delivering a part of the total dose by way of an implant.[109]

Time–dose data for patients with T3 lesions of the tonsillar fossa are shown in Figure 12-7*C* and again suggest the importance of overall treatment time.[115]

The rate of local control for T3 lesions involving the adjacent tongue, treated with once-a-day or twice-a-day fractionation, alone or followed by a radium needle implant boost to the primary site, is shown in Table 17-9 in Chapter 17. There was an improvement of 20 percentage points (35% improvement) in local control among the group of patients who received an interstitial boost. There were too few patients with T1–2 lesions, T4 lesions, or T3 lesions without base of tongue involvement treated with a radium needle boost to make such comparisons. For patients who received an interstitial boost, the incidence of mild and moderately severe complications of bone and soft tissue was twice as high as in patients treated with external beam alone (mild, 37% versus 20%; moderate, 7% versus 3%). The incidence of

TABLE 12-3. Local Control of T3–4 Squamous Cell Carcinomas of the Tonsillar Fossa (1954 to 1968)[158] and Base of Tongue (1954 to 1971)[163] Treated With High-Dose Megavoltage Irradiation at More Than 1000 cGy/wk

T Stage	Tonsillar Fossa Lesions Receiving > 6500 cGy at ≥ 1000 cGy/wk	Base of Tongue Lesions Receiving ≥ 7000 cGy at ≥ 1000 cGy/wk
T3		10/12 (83%)
T4		2/2 (100%)
T3–4	14/16 (88%)	
TOTAL	14/16 (88%)	12/14 (86%)

Note: M. D. Anderson Hospital data.

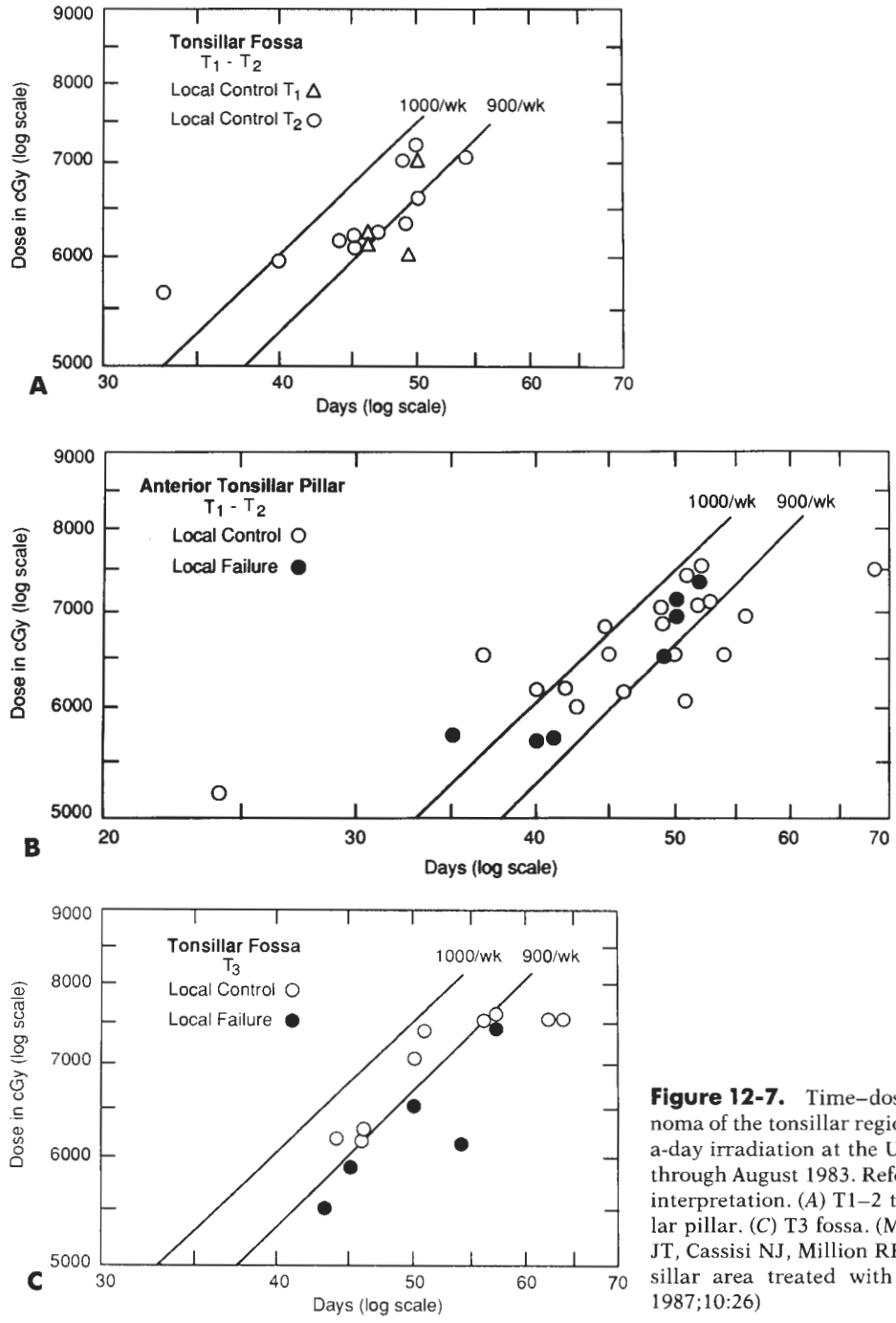

Figure 12-7. Time–dose distributions for squamous cell carcinoma of the tonsillar region treated with continuous-course once-a-day irradiation at the University of Florida from October 1964 through August 1983. Reference lines have been added for ease of interpretation. (*A*) T1–2 tonsillar fossa. (*B*) T1–2 anterior tonsillar pillar. (*C*) T3 fossa. (Modified from Mendenhall WM, Parsons JT, Cassisi NJ, Million RR. Squamous cell carcinoma of the tonsillar area treated with radical irradiation. Radiother Oncol 1987;10:26)

severe complications (2%) in the implanted patients was not increased compared with external beam alone (4%).

Base of Tongue

Local control results (2 years' minimum follow-up) according to T stage for patients who received external-beam irradiation alone to the primary site at the University of Florida between October 1964 and September 1981 are shown in Table 12-5.[63] Fifty-nine (89%) of 66 evaluable patients received treatment by once-a-day irradiation.

A time–dose scatter distribution for patients with T2–3 lesions is shown in Figure 12-8.[63] A time–dose relation is apparent.

Foote and associates[57] compared the results of continuous-course external-beam irradiation alone from the University of Florida and M.D. Anderson Hospital with the results of external beam plus an interstitial implant from six reported series. The authors concluded that the control results of external-beam irradiation alone were slightly better than those reported in the implant series for T1, T2, and T3 disease. For T4 lesions, the results favored the implant series. However, as pointed out by

TABLE 12-4. Local Control After Irradiation According to Site Within the Tonsillar Region

	Tonsillar Fossa			Anterior Tonsillar Pillar		
Institution	T1	T2	Total	T1	T2	Total
University of Florida[115]	4/4	17/18	21/22 (95%)*	5/7	18/26	23/33 (70%)*
M. D. Anderson[65]	15/15	31/32	46/47 (98%)†	23/27	71/87	94/114 (82%)†
University of California at San Francisco[125]	3/4	13/17	16/21 (76%)‡	2/6	12/24	14/30 (47%)‡
Massachusetts General[188]	9/11	43/72	52/83 (63%)§	5/7	21/46	26/53 (49%)§

* $P = .019$
† $P = .009$
‡ $P = .03$
§ $P = .08$

the authors (and as evidenced by the small number of patients with T4 disease who were treated by implant in the six series), there is considerable selection of patients for implantation. Some T4 tumors involve tissues that cannot be readily implanted (eg, the infrahyoid strap musculature).

The incidence of bone exposure and soft tissue necrosis according to boost technique for patients treated with continuous-course, external-beam irradiation alone at the University of Florida is shown in Table 12-6.[57] There was an 18% incidence of mild complications, a 6% incidence of moderate complications, and a 1% incidence of severe injuries. No moderate or severe complications were observed in 25 patients treated by twice-a-day irradiation. In the past, interstitial implantation with radium resulted in a 30% (8 of 27 patients) rate of bone and soft tissue injuries.[63]

TABLE 12-5. Base of Tongue: Local Control After External-Beam Irradiation Alone According to Treatment Technique and T Stage*

	Treatment Course	
Stage	Split Course	Continuous Course
T1	2/3	2/3
T2	0/1†	12/14 (86%)†
T3	4/8†	12/13 (92%)†
T4	1/12 (8%)	3/12 (25%)

* 59 patients received treatment by once-a-day irradiation; 7 received twice-a-day treatment.

† Four (44%) of 9 T2–3 lesions were controlled following split-course external-beam irradiation versus 24 (89%) of 27 T2–3 lesions treated by continuous-course irradiation ($P = .012$, using Fisher's exact test procedures).[110]

Note: University of Florida, October 1964 to September 1981.

(Modified from Gardner KE, Parsons JT, Mendenhall WM, Million RR, Cassisi NJ. Time–dose relationships for local tumor control and complications following irradiation of squamous cell carcinoma of the base of tongue. Int J Radiat Oncol Biol Phys 1987;13:509)

Soft Palate

Time–dose data for T1–2 patients with squamous cell carcinoma of the soft palate who received treatment with continuous-course once-a-day external-beam irradiation alone are shown in Figure 12-9.

Pyriform Sinus

Time–dose data for T1–2 pyriform sinus patients who received radical irradiation with continuous-course once-a-day irradiation at the University of Florida are shown in Figure 12-10.

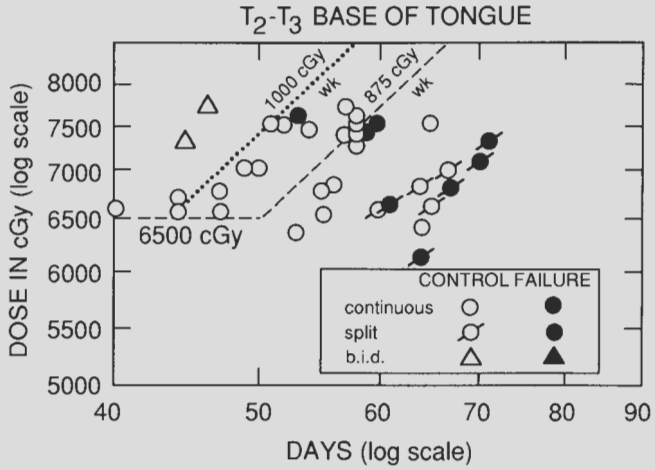

Figure 12-8. Time–dose scattergram for local control of T2–3 lesions of the base of the tongue following external-beam irradiation alone. The diagonal dotted line represents treatment administered at 1000 cGy per week, and the slashed line indicates treatment at 875 cGy/wk. These lines have been added as reference lines only. They are not meant to represent isoeffect lines. For those patients treated to more than 6500 cGy (*horizontal dashed line*) at greater than or equal to 875 cGy/wk (*diagonal dashed line*), local control was achieved in 17 of 18 patients (94%) versus 11 of 18 patients (61%) for those whose time–dose schedules fell outside of these ranges ($P = .019$).

TABLE 12-6. Base of Tongue Cancer: Bone Exposure and Soft Tissue Necrosis After Continuous-Course, External-Beam Irradiation Alone to the Primary Lesion According to Boost Technique

		Bone Exposure			Soft Tissue Necrosis		
Boost Technique	Patients*	Mild	Moderate	Severe	Mild	Moderate	Severe
Lateral	50	1 (2%)	0	1 (2%)	6 (12%)	1 (2%)	0
Submental	34	2 (6%)	1 (3%)	0	6 (18%)	3 (9%)	0
TOTAL	84	3 (4%)	1 (1%)	1 (1%)	12 (14%)	4 (5%)	0

* Two patients who developed both bone exposure and soft tissue necrosis were scored twice.
Note: University of Florida, October 1964 to July 1986.
(Foote RL, Parsons JT, Mendenhall WM, Million RR, Cassisi NJ, Stringer SP. Is interstitial implantation essential for successful radiotherapeutic treatment of base of tongue carcinoma? Int J Radiat Oncol Biol Phys 1990;18:1296)

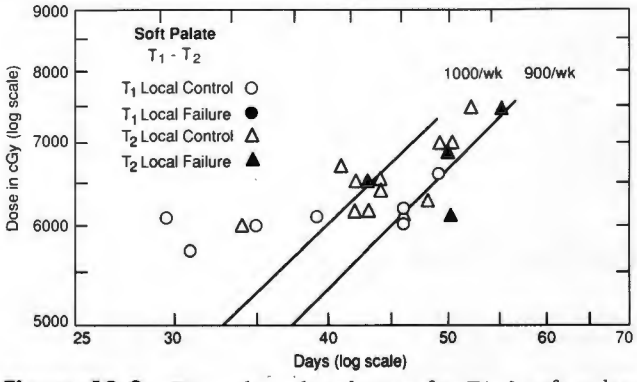

Figure 12-9. Time–dose distribution for T1–2 soft palate cancer following once-a-day irradiation at the University of Florida.

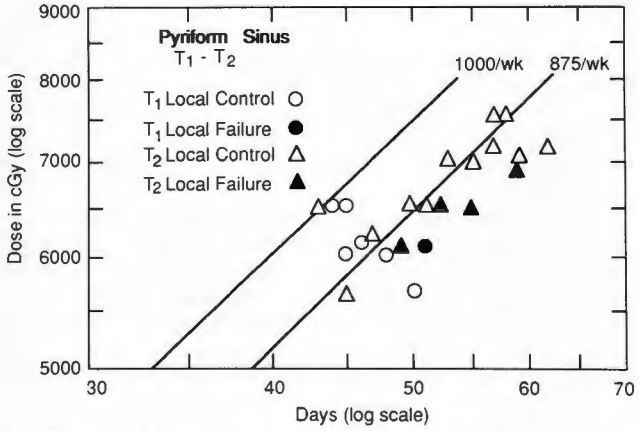

Figure 12-10. Time–dose distribution for local control of T1–2 pyriform sinus cancer following radical, continuous-course, once-a-day irradiation at the University of Florida.

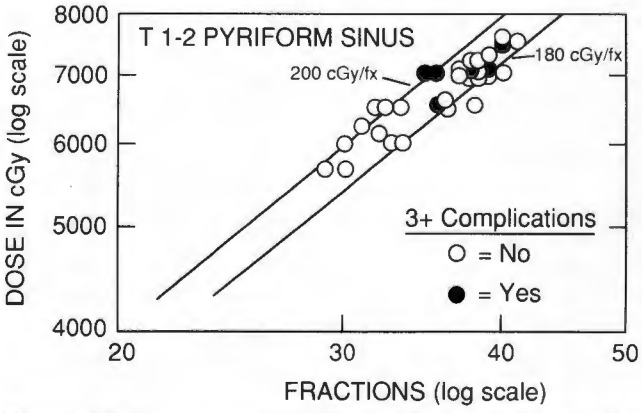

Figure 12-11. Severe complications for patients with T1–2 lesions of the pyriform sinus treated with continuous-course irradiation, once-a-day fractionation, with the primary site continuously disease-free. The lines are not isoeffect lines and are for reference purposes only. University of Florida data; patients treated October 1964 through March 1984; analysis March 1986. (Mendenhall WM, Parsons JT, Cassisi NJ, Million RR. Squamous cell carcinoma of the pyriform sinus treated with radical radiation therapy. Radiother Oncol 1987;9:205)

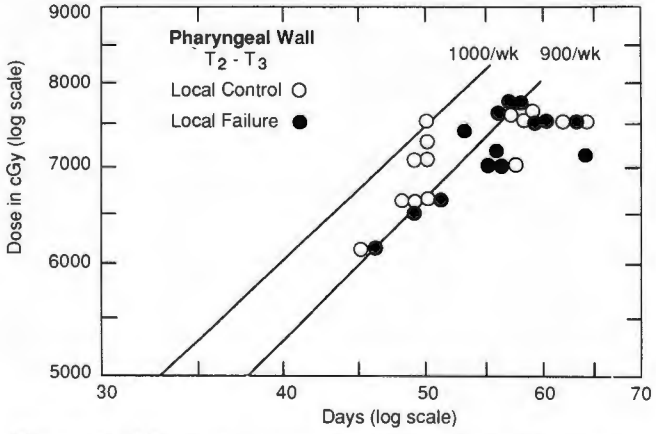

Figure 12-12. Local control for T2–3 lesions of the pharyngeal wall treated with external-beam irradiation alone, once-a-day fractionation. The lines represent treatments at 1000 and 900 cGy/wk. They are not isoeffect lines and are for reference purposes only. (Modified from Mendenhall WM, Parsons JT, Mancuso AA, Cassisi NJ, Million RR. Squamous cell carcinoma of the pharyngeal wall treated with irradiation. Radiother Oncol 1988;11:207)

The control rates are higher in patients whose treatments were administered in shorter overall treatment times. Severe complications after continuous-course once-a-day irradiation for patients with T1–2 lesions whose primary site remained continuously disease-free are shown in Figure 12-11.[114] All but one of the complications occurred at doses of 7000 to 7500 cGy, including both patients who received 7000 cGy in 7 weeks (200 cGy per fraction). All six patients who developed severe complications had T2 lesions.

Pharyngeal Wall

Time–dose data after continuous-course once-a-day irradiation for T2 and T3 squamous cell carcinomas of the pharyngeal wall are shown in Figure 12-12.[116] Treatment times greater than 7 weeks are associated with a high local failure rate, regardless of the total dose.

ALTERED FRACTIONATION SCHEMES

The relation between time and dose may be altered by (1) changing the instantaneous dose rate (ie, the number of centigrays administered per minute during an individual treatment); (2) varying the overall treatment time (ie, the number of days between the first and last treatment); or (3) varying the time (hours or days) between successive doses of irradiation. Despite considerable preoccupation with time–dose relations in radiation therapy, there are still no generally accepted optimum treatment schedules. The literature is replete with clinical trials, retrospective reviews, and experiments with fractionation schemes. The data are confusing and often conflicting. To understand the rationale for altering a fractionation scheme, one must first have some appreciation of the radiobiologic basis for using fractionated treatment.

Radiobiologic Basis for Fractionated Irradiation

When treatment is given in many fractions over a few weeks, a higher dose is necessary to accomplish a given effect than when treatment is given in a few fractions in a few days. The increase is due to two factors: the repair of sublethal injury and the repopulation of tumor cells.

Improvement in the therapeutic ratio is sought because the fractionation schedule used in most departments (five 180- to 200-cGy treatments per week) may be suitable in many clinical circumstances but is not optimal for every cancer. A number of treatment schemes have been devised in an attempt to (1) exploit differential sensitivities between normal tissues and tumor, (2) increase the possibility of irradiating cells in a sensitive phase of the cell cycles, (3) overcome the effect of hypoxia, and (4) limit the effect of tumor proliferation during treatments.

Attempted Calculation of Biologically Equivalent Treatment Schedules

Radiation therapists have for many years tried to devise abbreviated treatment schedules that would produce end results equivalent to fractionation schemes using five fractions per week. A number of methods have been developed to predict these supposedly equivalent doses, the best known of which is the nominal standard dose (NSD) formula of Ellis.[43]

The NSD equation was itself mathematically and conceptually complex. It was estimated that, in the hands of clinicians, it was misused about half the time.[130] Because of its complexity, Orton and Ellis[131] produced tables based on a mathematical simplification of the NSD concept. These tables contained TDF (time, dose, fractionation) factors whereby various fractionation schemes might be compared or equated. Although the tables were easier to use and largely eliminated the problem of mathematical errors, they introduced a new problem, namely, that they did not require the physician to think about late versus early reactions and proliferation rates of tumors. In principle, the physician could devise any number of treatments that supposedly would result in the same biologic end point. For instance, 6300 cGy in 28 fractions over 5½ weeks (5 fractions per week) would, according to the TDF tables, be equivalent to 3720 cGy in 4 fractions over 4 weeks (1 fraction per week), or to 4600 cGy in 10 fractions over 3½ weeks (3 fractions per week). Many clinical misadventures resulted from use of the NSD formula and TDF tables. The formula did not accurately predict late damage to normal tissues when small numbers of large-dose fractions were used. The importance of the time factor for tumors was underestimated, whereas it was overestimated for late normal-tissue reactions. Based on these problems as well as the observed clinical disasters that resulted from its use, the *NSD formula and its TDF derivatives should no longer be used.*[60]

Consequences of Experimental Fractionation Schemes: Dissociation Between Acute and Late Effects

In 1962, at the M.D. Anderson Hospital, the treatment schedule for breast cancer was changed from five to three fractions per week; cobalt-60 was used in both patient groups. By adjusting the number of treatments given with bolus, it was possible to produce identical acute skin reactions in the two treatment groups. Despite equal acute reactions, the late effects of the two regimens differed markedly. Late complications in the group given three fractions per week were said to be horrendous.[174] Subsequently, many other clinical investigators have shown a large increase in late complications, with little or no difference in acute reactions, when treatment regimens were changed to fewer, larger-dose fractions. These data suggest that the dose–survival characteristics of the target cells responsible for producing late effects differ from those of the target cell responsible for acute effects.

This means that with x-rays, as one reduces the size of the dose per fraction, one achieves a differential sparing of late-effects tissues (eg, brain, spinal cord, bone, cartilage) relative to acute-effects tissues (eg, skin, oral mucosa, gut epithelium). Conversely, as the fraction size is increased, the total dose must be reduced more to main-

tain equal late effects than to maintain equal early effects.

This dissociation has been interpreted as a difference in repair capacity (or shape of the shoulder of the dose survival curves) between early- and late-responding normal tissues. Over at least a limited range, possibly up to 1000 cGy, survival curves can be fitted to the linear quadratic equation:

$$\text{Surviving fraction} = e^{(-\alpha d - \beta d^2)}$$

where: α describes the slope of the initial (single-hit) portion of the cell survival curve; β describes the slope of the terminal (multiple-hit) portion of the curve; d = dose

The ratio α/β is therefore a measure of susceptibility to killing by single-hit versus multiple-hit mechanisms. It is tissue-specific. The actual number α/β is the dose in grays at which killing by single-hit mechanisms (α injury) is equal to killing by multiple-hit mechanisms (β injury).

For virtually every tissue studied, α/β values for late-effects tissues are consistently lower (eg, 2 to 4 Gy) than for acute-effects tissues (eg, 9 to 12 Gy). Since α/β describes the relative shapes of the initial and terminal portions of the survival curve, it can be inferred that those tissues with low α/β ratios (ie, late-effects tissues) have curvier cell survival curves than tissues with high α/β values (acute-effects tissues). The differences in the shapes of the cell-survival curves for acute- and late-responding tissues are shown in Figure 12-13. If α/β ratios relate to proliferative activity of tissues (ie, low values for slowly proliferating or nonproliferative tissues such as spinal cord and high values for rapidly proliferating tissues such as gut epithelium), then one would expect most tumors to have high values. This in fact appears to be the case.

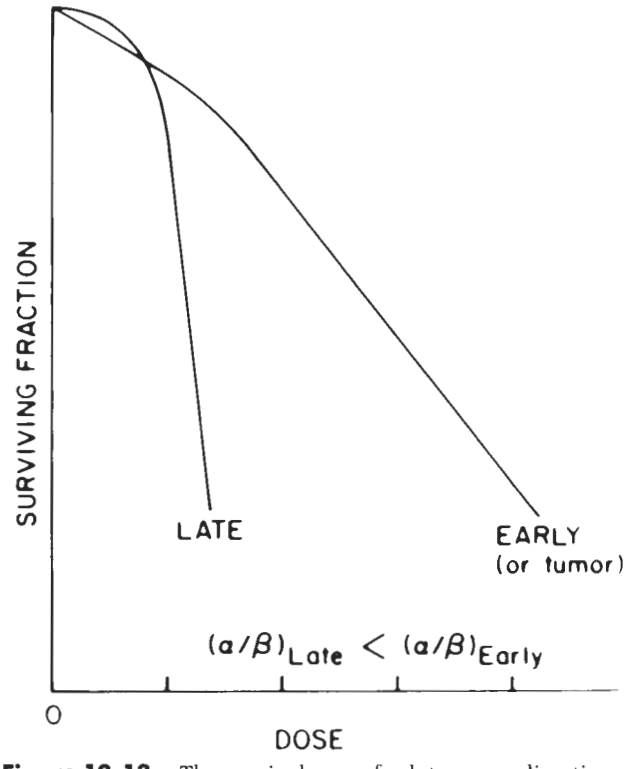

Figure 12-13. The survival curve for late-responding tissues is more curved than for early-responding tissues.

Armed with the knowledge of differing sensitivities to changes in dose fractionation between acute-effects (or tumor) and late-effects tissues, as well as with information about tumor proliferation, reoxygenation, and redistribution through the cell cycle, the next step is to determine how best to exploit the differences.

Hypofractionation

Starting around the 1960s, modifications of conventional fractionation schemes were made for both physician and patient convenience and usually consisted of a small number of fractions, each usually larger than 250 cGy, so-called hypofractionation. With the exception of a few reports from England[19,148] and the University of Maryland,[161] a large body of literature associates this approach with a high incidence of severe late effects. This is true despite the fact that in most of the hypofractionation studies the overall treatment times were protracted for 6 weeks or more, indicating that *fraction size and total dose are the important determinants of late effects, whereas overall treatment time has little influence.*

Treatment With One or Two High-Dose Fractions

In the most extreme form of hypofractionation, single massive doses were administered in hopes of producing a caustic effect or slough of tissue analogous to a surgical excision. Originally developed in the early years (from 1900 through the 1920s) of radiation therapy, the technique was generally abandoned, but it was sporadically revived by a few physicians in subsequent years for a variety of reasons.[10] In 1965, Andrews reported disastrous results of single-dose treatment (2000 to 2750 R) in 20 patients with early and moderately advanced head and neck squamous cell carcinomas treated at the National Cancer Institute.[4] Tumor control was infrequent and complications were frequent, severe, and sometimes fatal.

Rubenfeld, at Bellevue Hospital, New York City, reported a similar negative experience with 1500 R given on each of two successive days for head and neck cancer.[149] Severe and fatal complications led to abandonment of the technique.

Rapid fractionation schemes for other tumor systems have also produced unexpected, severe complications.[8,40]

A dose of 2000 cGy delivered in two 1000-cGy fractions with a 7- to 10-day interval has often been used at the University of Florida for palliation of head and neck squamous cell carcinoma. No complications have been observed; survival time in most patients selected for this therapy is short because of the advanced nature of their tumors. A reduction off the spinal cord is sometimes made for the second treatment.

Treatment With One or Two Fractions Per Week

Harrison and coworkers[74] reported the results of treatment of early (Tis, T1, T2) vocal cord cancer at the Peter MacCallum Cancer Institute, Melbourne, Australia, where from 1969 to 1985 there were 131 patients who were treated with 6000 cGy in 30 fractions over 6 weeks and 66 others who received 4200 to 4620 cGy in 7 frac-

tions, 600 to 660 cGy per fraction, given once a week.[74] The TDFs in the two treatment schemes were the same. When one considers that the weekly tumor dose was only 600 to 660 cGy in the patients in the unconventional treatment group, it is not surprising that this group had fewer acute side effects. For presumably the same reason (low weekly rate of dose accumulation), the local tumor control rates for Tis and T1 lesions were also significantly lower ($P = .06$) in the patients who received treatment once a week. Of note were 15 severe complications (23%) in 65 evaluable patients treated with the hypofractionated regimen.

Handa and coworkers[73] performed a randomized trial comparing two versus five fractions a week (6000 to 6500 cGy over 6 to 6½ weeks) for oral cavity cancers. The NSDs were equivalent, and overall treatment times were identical. The treatment with five fractions per week was judged superior in terms of both tumor control and late effects.

Dische and associates[37] treated advanced lung cancer with 3400 to 3600 cGy in six fractions (twice weekly) over 18 days. Eight (11%) of 70 patients who survived 6 months developed myelopathy.

Sause and coworkers[153] reported unacceptable late skin changes in over half of their patients with breast cancer whose chest-wall treatment consisted of 4000 cGy in 10 fractions (400 cGy twice a week for 5 weeks).

In a prospective study by Turesson and Notter,[177] bilateral parasternal irradiation was administered after mastectomy. Each patient served as her own control: the right field received daily treatment (216 cGy per fraction for 16 fractions over 22 days) and the left received once-a-week treatment (621 cGy per fraction for 4 fractions over 22 days). Acute skin erythema was equal as measured by reflectance spectrophotometry. At 5 years, half of the patients treated with the once-a-week schedule, compared with none of the conventionally treated patients, developed marked telangiectasia ($P < .001$). In another prospective study comparing daily versus twice-a-week irradiation, the authors reached the same conclusions.[178]

Treatment With Three Fractions Per Week

Between 1965 and 1975 at the Medical College of Wisconsin, two different dose schedules, using either 3 or 5 fractions per week, were used in the treatment of patients with squamous cell carcinomas of the oral cavity and oropharynx.[28] Treatments were equated by the NSD formula and delivered 6000 to 7200 cGy in 30 to 36 fractions (5 fractions per week) versus 5400 to 7200 cGy in 18 to 24 fractions (3 fractions per week). Local treatment results for 69 patients with oropharyngeal cancers are given in Table 12-7. Despite what the authors considered a higher proportion of unfavorable tumor sites (base of tongue and pharyngeal wall) in the group given 5 fractions per week, local control was much better when 5 fractions per week were used. The results for oral cavity were also superior in the group given 5 fractions per week.

Kok[89] experimented with a variety of fractionation schemes for stage I carcinoma of the larynx. His results for three versus five fractions per week are summarized in Table 12-8. Despite lower TDFs, the patients treated with five fractions per week had a higher rate of tumor control. Acute reactions were less severe, whereas, above a certain fraction size, late effects were much more severe in the patients receiving three fractions per week. Kok concluded that by increasing the interval between fractions to 48 hours, both the normal epithelium and tumor were relatively spared by repopulation, but the nonproliferative connective tissues were not.

TABLE 12-7. Local Control After Irradiation of Oropharyngeal Cancer With Three Versus Five Fractions per Week With Equivalent Nominal Standard Dose

	Local Control	
T Stage	Three Fractions per Week*	Five Fractions per Week†
T1–2	3/10 (30%)	17/19 (89%)
T3	0/5	6/11 (55%)
T4	0/11	5/13 (38%)

* Three fractions per week group: 9/26 (35%) were base of tongue or pharyngeal wall primary lesions.

† Five fractions per week group: 27/43 (63%) were base of tongue or pharyngeal wall primary lesions.

Note: Medical College of Wisconsin data.

(Modified from Byhardt RW, Greenberg M, Cox JD. Local control of squamous carcinoma of the oral cavity and oropharynx with 3 versus 5 treatment fractions per week. Int J Radiat Oncol Biol Phys 1977;2:418. Copyright © 1977, Pergamon Press, Ltd)

Between 1963 and 1975, the British Institute of Radiology conducted a randomized trial of three versus five fractions per week for 734 patients with cancers of the laryngopharynx. A number of dose schedules were employed. Total doses were 11% to 13% higher in the patients treated with five fractions per week, and time–dose fractionation values were nearly identical. No differences in acute and late reactions were noted for the entire series.[193,194] In the subgroup of patients with T1N0 vocal cord cancers, the 10-year laryngectomy-free rate for the group that received five fractions per week was significantly higher than for the group that received three fractions per week ($P = .05$).[194]

Treatment With Four Fractions Per Week

Thomas and associates reviewed the 1981 to 1982 results from the treatment of oropharyngeal cancer at

TABLE 12-8. Treatment of Stage I Larynx Cancer With Three Versus Five Fractions per Week (The Hague, The Netherlands)

Treatment Group	Time, Dose, Fractionation Factor (Range)	Local Control (3 Years)
Five fractions per week*	100–107	16/18 (89%)
Three fractions per week†	105–133	26/42 (62%)

* 6300 cGy in 30 to 33 fractions (190–210 cGy per fraction)

† 6300 cGy in 16 to 26 fractions (240–385 cGy per fraction)

(Data from Kok G: Influence of the size of the fraction dose on normal and tumour tissue in ^{60}Co radiation treatment of carcinoma of the larynx and inoperable carcinoma of the breast. Radiol Clin Biol 1971;40:100–115)

the Institut Gustave-Roussy.[175] Sixty-three patients were treated in 1981 with 200-cGy fractions, 5 days a week, to 7000 cGy in 7 weeks. In 1982, because of a shortage of treatment facilities, the schedule was changed to 250 cGy per fraction, 4 days a week, also to a total dose of 7000 cGy in 7 weeks. Prognostic factors were equally distributed. No differences in local–regional control or acute effects were observed. However, soft tissue necrosis occurred twice as frequently ($P = .03$) and trismus occurred four times as frequently ($P = .01$) in patients treated with four fractions per week.

Protraction of Overall Treatment Time

Whereas late effects are little influenced by modifications of overall treatment time, proliferative tissues (acute-effects tissues and tumor) are markedly affected. The severity of acute effects depends on the weekly rate of dose accumulation, and the duration of those effects correlates with the total dose administered.

Excessively Protracted Continuous-Course Irradiation (14 Weeks)

In 1965, Andrews[4] reported the National Cancer Institute treatment results in 43 patients with head and neck squamous cell carcinomas who received 8000 to 10,000 R (mode, 9000 R) with 2-MV x-rays. The overall treatment time was usually 14 weeks with three fractions given per week (about 600 cGy/wk). Only 9 patients were cured, 5 of whom had early cancers of the vocal cord or nasopharynx. Failure to control moderately advanced and advanced cancers was almost uniform. Regeneration of clonogenic cells during the excessively prolonged treatment period apparently exceeded the ability of these high doses to produce cures.

Split-Course Irradiation (8 to 10 Weeks)

A variety of split-course techniques were popularized by Sambrook,[150,151] Holsti,[78] Marcial,[101] and Scanlon.[154,155] Usually, a planned 2- to 3-week rest period was introduced roughly midway through a treatment course that was otherwise conventional, or nearly so, in terms of total dose and daily fraction size. In some split-course schemes, the total dose was increased by 5% to 10% to compensate for the treatment interruption. At the University of Florida, where split-course irradiation was used almost routinely from mid-1969 through June 1974, no conscious attempt was made to increase the total dose to offset the split. Other investigators have not changed the total dose but have increased the daily fraction size. Some have used three instead of five fractions per week or occasionally more than one split in the treatment course.

Split-course irradiation was originally introduced to minimize acute side effects of a continuous course of treatment. Some authors also proposed that, because of continued regression during the rest interval and presumably better oxygenation during the second half of therapy, tumor control might actually be better after split-course treatment.

Between September 1964 and August 1976, 468 patients with previously untreated squamous cell carcinoma of the oral cavity, pharynx, and supraglottic larynx received curative courses of external-beam irradiation to their primary lesion at the University of Florida; some patients received a radium implant boost after external irradiation.[123,134] Two hundred fourteen patients were treated by split-course and 254 by continuous-course irradiation. Patients were not randomized. During the first 5 years of the study, almost all of the patients received continuous-course irradiation; in the succeeding 5 years, the split-course technique was used almost exclusively; then during the last 2 years continuous-

TABLE 12-9. Split-Course Versus Continuous-Course Irradiation: Local Control by Tumor Site and Treatment Technique: T1–2*

	External Beam		External Beam Plus Radium	
Disease Site	Split Course (6200 cGy)†	Continous Course (6100 cGy)†	Split Course (4700/2600 cGy)‡	Continuous Course (5000/2500 cGy)‡
Oral cavity§	4/8	2/5	8/11	8/13
Oropharynx	17/24	39/45	5/6	6/8
Nasopharynx	4/4	3/3	NA	NA
Hypopharynx	2/4	10/17	NA	NA
Supraglottic larynx	4/6	11/12	NA	NA
TOTAL‖	31/46 (67%)	65/82 (79%)	13/17 (76%)	14/21 (67%)

NA, no data available.

* 25 of 63 split-course irradiation patients (40%) had T1 lesions versus 36 of 103 continuous-course irradiation patients (35%) with T1 lesions.

† Median dose of external-beam irradiation.

‡ Median dose of external-beam irradiation and calculated interstitial radium dose.

§ Patients with oral cavity primary lesions who received all or more than half of the total tumor dose from interstitial irradiation were excluded.

‖ Total local control: split course, 44/63 (70%), versus continuous course, 79/103 (77%); $P = .20$.

Note: University of Florida data.

(Parsons JT, Bova FJ, Million RR. A reevaluation of split-course technique for squamous cell carcinoma of the head and neck. Int J Radiat Oncol Biol Phys 1980;6:1647. Copyright © 1980, Pergamon Press, Ltd)

TABLE 12-10. Split-Course Versus Continuous-Course Irradiation: Local Control by Tumor Site and Treatment Technique for T3 Tumors

	External Beam		External Beam Plus Radium	
Disease Site	Split Course (6600 cGy)*	Continuous Course (6600 cGy)*	Split Course (5600/2600 cGy)†	Continuous Course (5600/2600 cGy)†
Oral cavity	2/5	1/3	3/10	10/17
Oropharynx	9/22	8/15	3/6	10/19
Nasopharynx	5/6	3/3	NA	NA
Hypopharynx	2/11	5/7	NA	NA
Supraglottic larynx	4/4	4/7	NA	NA
TOTAL‡	22/48 (46%)	21/35 (60%)	6/16 (38%)	20/36 (56%)

NA, no data available.

* Median dose of external-beam irradiation.

† Median dose of external-beam irradiation and calculated interstitial radium dose.

‡ Total local control: split course, 28 of 64 (44%), versus continuous course, 41 of 71 (58%); $P = .07$.

Note: University of Florida data.

(Parsons JT, Bova FJ, Million RR. A reevaluation of split-course technique for squamous cell carcinoma of the head and neck. Int J Radiat Oncol Biol Phys 1980;6:1647. Copyright © 1980, Pergamon Press, Ltd)

course irradiation was used. Patients in the split-course group had a planned 14- to 16-day interruption after 2800 to 3000 cGy in 15 fractions. Patients in both groups received five 180- to 200-cGy fractions per week to the primary tumor. During the rest interval, the primary lesion regressed or stabilized; none enlarged. Metastatic neck nodes usually stabilized but occasionally regressed. Split-course patients reported alleviation of acute symptoms 10 to 12 days into the split; mucous membranes appeared normal when the patients resumed therapy.

Tables 12-9 through 12-11 show higher rates of local control after continuous-course irradiation, with the most marked differences noted in moderately advanced and advanced lesions. Results for T3 ($P = .07$) and T4 ($P = .08$) lesions were close to statistical significance.

Subclinical neck disease was controlled in all instances by both techniques. A significantly greater proportion of N1 ($P = .02$) and N2 ($P = .05$) neck disease was controlled by continuous-course irradiation (Table 12-12).

Five-year survival rates for patients treated with continuous-course irradiation were about 10 percentage points higher for all stages of disease. For stage III and IV disease the differences were significant ($P = .02$ and $P = .03$, respectively).[64] For patients with stage IV disease, a decline of 10 percentage points in the survival rate represented almost a 50% decrease in the probability of 5-year survival.

The rates of occurrence of soft tissue or bone complications in 315 patients with squamous cell carcinoma of the oral cavity or oropharynx did not differ significantly for the two treatment groups. This fits with the idea that late effects are relatively independent of overall treatment time. Routine use of the split-course scheme has

TABLE 12-11. Split-Course Versus Continuous-Course Irradiation: Local Control by Tumor Site and Treatment Technique for T4 Tumors

	External Beam		External Beam Plus Radium	
Disease Site	Split Course (6600 cGy)*	Continuous Course (6600 cGy)*	Split Course (6600/1400 cGy)†	Continuous Course (6100/2300 cGy)†
Oral cavity	NA	NA	NA	1/3
Oropharynx	1/18	2/7	0/2	1/2
Nasopharynx	2/6	6/10	NA	NA
Hypopharynx	1/8	0/6	NA	0/1
Supraglottic larynx	1/2	0/2	NA	NA
TOTAL‡	5/34 (15%)	8/25 (32%)	0/2 (0%)	2/6 (33%)

NA, no data available.

* Median dose of external-beam irradiation.

† Median dose of external-beam irradiation and calculated interstitial radium dose.

‡ Total local control: split course, 5 of 36 (14%), versus continuous course, 10 of 31 (32%); $P = .08$.

Note: University of Florida data.

(Parsons JT, Bova FJ, Million RR. A reevaluation of split-course technique for squamous cell carcinoma of the head and neck. Int J Radiat Oncol Biol Phys 1980;6:1648. Copyright © 1980, Pergamon Press, Ltd)

TABLE 12-12. Neck Control in Heminecks Treated by Split-Course Versus Continuous-Course Irradiation Alone

Neck Stage	Split Course (Heminecks)	Continuous Course (Heminecks)
N0	108/108 (100%)	158/158 (100%)
N1	11/16 (69%)	35/37 (95%)*
N2A–2B	11/23 (48%)	25/34 (74%)†
N3A	4/14 (29%)	2/7 (29%)

* $P = .02$, Fisher's exact test.[110]
† $P = .05$, X^2 test.[110]
Note: University of Florida data.
(Parsons JT, Bova FJ, Million RR. A reevaluation of split-course technique for squamous cell carcinoma of the head and neck. Int J Radiat Oncol Biol Phys 1980;6:1648. Copyright © 1980, Pergamon Press, Ltd)

been abandoned at the University of Florida. If for some reason treatment must be interrupted, the interruption should be kept as short as possible.

Although it is customary to think that the effects of a rest period can be overcome merely by increasing the total dose by 5% to 10%,[79] in a series by Overgaard and colleagues[133] of 92 patients with carcinoma of the larynx treated by split-course irradiation, a dose increase of 20% (1200 cGy) was required to achieve rates of tumor control equal to those after continuous-course irradiation. In the process of equalizing the control rates between the patients in the conventional group (5700 to 6000 cGy in 30 fractions over 6 weeks) and those in the split-course group (6800 to 7200 cGy in 34 to 36 fractions over 10 to 10½ weeks), a staggering increase in the incidence of late complications was noted, again showing that late effects are dependent on total dose and dose per fraction, but not overall treatment time. *Attempts to equalize control rates between split- and continuous-course treatment by increasing total dose result in an increased rate of complications in patients given split-course treatment.* Likewise, *attempts to equalize control rates between split- and continuous-course regimens by increasing the fraction size to maintain the same overall treatment time produce increased rates of late complications.* There are abundant examples in the literature to prove the point.

In the RTOG randomized trial for base of tongue cancer, split-course treatment (3000 cGy in 10 fractions, a 3-week split, then 3000 cGy in 10 fractions) resulted in no significant differences in 5-year survival, local control, or regional control rates compared with continuous-course irradiation (6000 to 6600 cGy over 6 to 7 weeks), but the total number of patients with some type of necrosis (cartilage, skin, bone, or soft tissue) was about twice as great in the split-course group.[102] In the RTOG randomized trial for cancer of the nasopharynx, split-course treatment (3000 cGy in 10 fractions, a 3-week split, then 3000 cGy in 10 fractions) resulted in no differences in local control, disease-free survival, or survival compared with continuous-course irradiation (6000 to 6600 cGy over 6 to 7 weeks), but the incidence of myelitis or other neuropathy in the split-course group (8 of 55, or 15%) was 2½ times as great as in the continuous-course group (3 of 54, or 6%).[101] Hypofractionated split-course regimens appear to be a step in the wrong direction.

Effect of Overall Treatment Time on Tumor Control

In an analysis of 310 patients with T3–4, N0 squamous cell carcinomas of the larynx, Maciejewski and associates[97] found a strong dependence of local control on overall treatment time, especially between 4 and 7 weeks, but no dependence on dose per fraction or number of fractions. Late damage to normal tissues depended on dose per fraction and number of fractions but not on overall treatment time. In an analysis of 498 patients with oral cavity or oropharyngeal squamous cell carcinomas, the same conclusions were reached.[98] Furthermore, the probability of local control correlated with the severity of acute mucositis, suggesting that excessive protraction of treatment to minimize acute toxicity compromises local control. This is not surprising since both tumor control and severity of acute reactions are functions of total dose and rate of dose accumulation.[99]

In multivariate analyses of factors predictive of tumor control, Bataini and coworkers[16] found that for patients who received more than 5500 cGy, the only treatment factor that significantly influenced neck node control ($P = .002$)[16] and control of cancer of the tonsillar region ($P < .0001$)[15] was overall treatment time. Above 5500 cGy, the total dose was not significantly correlated with tumor control.

Withers and associates[197] suggest that accelerated clonogen repopulation begins 3 to 5 weeks after initiating treatment and that a dose increment of about 60 cGy/d is required to compensate for this repopulation. The idea of a 4-week lag period during which time no additional dose is required to compensate for the effects of proliferation is consistent with observations made in rodent[34,126] and human[179] skin.

Because of the evidence that prolonged overall times lead to worse tumor control, it is logical to investigate shorter overall treatment times. In the following section, various strategies are discussed.

Hyperfractionation

We have seen that, with x-rays, as the size of the dose per fraction is reduced, differential sparing of late effects relative to acute effects occurs. By reducing the size of the dose per fraction, it is possible to exploit the differences in the shapes of the dose–response curves such that the two curves are favorably separated from one another (Fig. 12-14).[58]

This forms the basis for *hyperfractionation.* By definition, hyperfractionation refers to delivery of a large number of smaller-than-conventional fractional doses in an overall treatment time that is similar to that for delivery of conventional fractional doses, accomplished by delivering more than one fraction per day. The total dose is generally slightly higher than the conventional total dose to increase the probability of tumor control for an equal level of late effects. Other benefits that might occur owing to an increased number of small-dose fractions would be (1) an increased probability of irradiating redistributing tumor cells in a sensitive phase of the cell cycle (versus nonproliferating connective tissues, which would not be affected by redistribution between treatments[195]) and (2) perhaps less dependence of smaller-dose fractions on the presence of molecular oxygen.

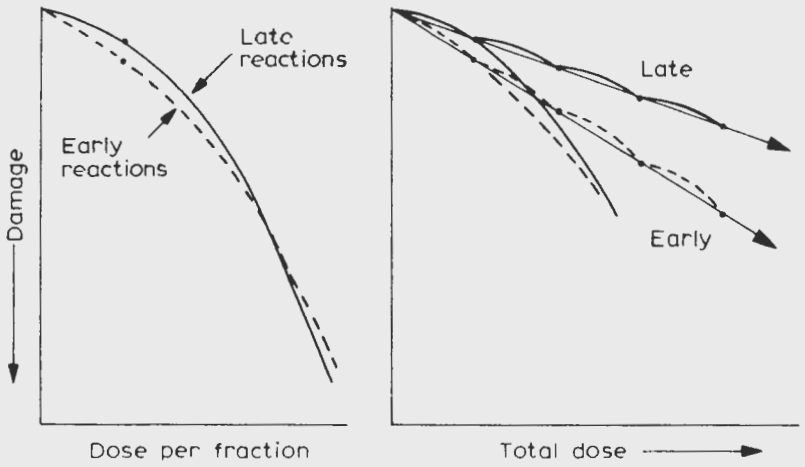

Figure 12-14. The figure on the left shows the differences in the shapes of the dose–response curves for early (or tumor) versus late effects. The curves on the right show that by fractionating the dose into multiple small increments it is possible to produce a favorable separation between the early- and late-effects curves. Reduction in size of the dose per fraction decreases the slope of the fractionated response curve more for late than for acute effects. (Fowler JF: The Second Klaas Breur Memorial Lecture: La Ronde—radiation sciences and medical radiology. Radiother Oncol 1983; 1:9)

Because late-responding tissues do not regenerate during treatment, the only way that they can survive successive doses of radiation is through repair of sublethal damage. It is critical therefore that the intervals between fractions be sufficient to allow such repair to be complete or nearly so, since insufficient intervals would negate the benefits of small dose fractions. In the University of Florida twice-a-day experience, a minimum 4-hour interfraction interval (which was based on calculations of half-lives to repair sublethal damage in vitro or in acutely responding tissues in vivo) has generally been used. Newer evidence indicates that early- versus late-responding tissues differ not only in repair capabilities but also in the time that it takes to repair damage. In several late-effects tissues that have been studied, repair takes considerably longer than for early-effects tissues.[6,107,185] It generally becomes impractical to space dose fractions longer than 6 to 8 hours apart; at the University of Florida, the minimum interval is now 6 hours. The time intervals between fractions are therefore 18 hours for half the treatments and 6 hours for the other half. If treatment is given more frequently than twice a day, the deleterious effects of insufficient interfraction intervals are magnified.

Isoeffect formulas give an estimate of relative late effects, acute effects, and tumor effects to help the therapist choose the appropriate total dose when changing from one fractionation scheme to another.[60,198] One must exercise caution and judgment in their use. This is particularly true for late-effects tissues, which have a low α/β value; as the fraction size is reduced, for example, from 200 cGy to 120 cGy, the formulas predict that it might be permissible to increase the total dose by 20% to 25% and still maintain an equal level of late effects. Because of their nature, the formulas are sensitive to small errors for tissues with low α/β values and could result in serious underdosage or overdosage. Although theoretically one might achieve additional sparing of late-effects tissues with fractions smaller than 120 cGy, there are no clinical data to prove the point and there are animal data showing that the additional sparing of the spinal cord obtained by reducing the dose per fraction from 200 to 100 cGy is less than predicted by the linear quadratic model. The use of α/β ratios (which are extrapolated from data involving large dose fractions) to design new dose schedules with fraction sizes below 200 cGy should be done cautiously.[184]

Remembering the disastrous consequences in the past when the NSD formula was used to extrapolate into the range of high-dose fractions (for which few clinical data were available), today's practitioner should be cautious (lest history repeat) in using the linear-quadratic formula to extrapolate into the range of low-dose fractions, for which there are also few data.

University of Florida Experience

A twice-a-day treatment schedule has been used at the University of Florida to manage moderately advanced and advanced squamous cell carcinomas of the head and neck since March 1978. Between March 1978 and March 1989, 419 patients with 439 primary cancers (including 20 patients with simultaneous lesions) received twice-a-day irradiation alone to the primary site, with or without the addition of a planned neck dissection 4 to 6 weeks after irradiation. All patients had follow-up for at least 2 years or until death (analysis, March 1991). Doses ranged from 7440 to 8160 cGy over 6 to 7 weeks by continuous-course treatment (5 days per week) using 120 cGy twice a day. Fifty-four (28%) of 192 patients with oropharyngeal tumors received an additional dose of 1000 to 1500 cGy from an interstitial implant (usually with radium) after the basic external-beam dose. The dose to the spinal cord was limited to 4560 cGy in 38 fractions over 19 treatment days. The low neck and posterior electron strips (when required) were treated once a day. No patients had chemotherapy as part of their initial management. Seventy-nine percent of patients had stage III or IV disease (47% stage IV).

ACUTE EFFECTS. Most patients developed confluent mucositis after 2½ to 3 weeks of treatment. Mucositis usually resolved within 4 to 6 weeks after completing treatment. In a small number of patients, complete mucosal healing required 2½ to 3 months. Sixty-six patients (16%) had acute reactions of such severity that they required or were recommended to receive feeding by nasogastric or gastrostomy tubes; eight patients (2%) required hospitalization for 7 to 14 days in the postirradiation period for intravenous hydration. Five patients

(1%) required unplanned treatment interruptions after doses of 3350, 4800, 5800, 5800, and 6720 cGy, respectively. Three patients required tracheostomy (one each after 240 and 2000 cGy because of stridor; one after 6960 cGy because of aspiration). Two fatal complications occurred during the immediate postirradiation period; one was related to inadvertent overdosage of the wrong intravenous medication, and the other resulted from severe dehydration, aspiration pneumonia, and renal failure.

RESULTS AND COMPLICATIONS OF TREATMENT. All of 16 T1 lesions (4 base of tongue, 7 tonsillar region, 2 pharyngeal wall, 1 oral tongue, 2 supraglottic larynx) were locally controlled.

Local control results of continuous-course once-a-day treatment at the University of Florida are compared with those of twice-a-day irradiation for cancers of the oropharynx, hypopharynx, and larynx in Tables 12-13 through 12-15, respectively. For T2, T3, and T4 cancers of the larynx and hypopharynx, there were increases of 15

TABLE 12-13. Oropharyngeal Cancer: Comparison of Local Control (Minimum 2-Year Follow-Up) According to Treatment Schedule (Continuous Course, Once-a-Day Versus Twice-a-Day)

	T2		T3		T4	
Primary Site	Once-a-Day	Twice-a-Day	Once-a-Day	Twice-a-Day	Once-a-Day	Twice-a-Day
Tonsil	14/14	9/11 (82%)	NA	NA	NA	NA
Anterior tonsillar pillar	17/24 (71%)	15/21 (71%)	NA	NA	NA	NA
Tonsillar region	NA	NA	14/20 (70%)	24/33 (73%)	4/11 (36%)	6/11 (55%)
Base of tongue	14/20 (70%)	13/14 (93%)	15/18 (83%)	14/18 (78%)	2/12 (17%)	5/13 (38%)
Soft palate	14/19 (74%)	8/8	4/9 (44%)	5/9 (56%)	1/3	0/1
TOTAL	59/77 (77%)*	45/54 (83%)*	33/47 (70%)	43/60 (72%)	7/26 (27%)†	11/25 (44%)†

NA, no data available.
* $P = .24$
† $P = .16$
Note: University of Florida data; analysis March 1991.

TABLE 12-14. Hypopharyngeal Cancer: Comparison of Local Control (Minimum 2-Year Follow-Up) According to Treatment Schedule (Continuous Course, Once-a-Day Versus Twice-a-Day)

	T2		T3		T4	
Primary Site	Once-a-Day	Twice-a-Day	Once-a-Day	Twice-a-Day	Once-a-Day	Twice-a-Day
Pyriform sinus	12/16 (75%)	9/9	1/3	2/3	0/2	0/1
Pharyngeal wall	8/17 (47%)	8/10	8/21 (38%)	8/12	1/8	1/3
TOTAL	20/33 (61%)*	17/19 (89%)*	9/24 (38%)†	10/15 (67%)†	1/10	1/4

* $P = .03$
† $P = .07$
Note: University of Florida data; analysis March 1991.

TABLE 12-15. Laryngeal Cancer: Comparison of Local Control (Minimum 2-Year Follow-Up) According to Treatment Schedule (Continuous Course, Once-a-Day Versus Twice-a-Day)

	T2		T3		T4	
Primary Site	Once-a-Day	Twice-a-Day	Once-a-Day	Twice-a-Day	Once-a-Day	Twice-a-Day
Vocal cord	81/108 (75%)	26/28 (93%)	7/13 (54%)	19/28 (68%)	NA	3/7
Supraglottic larynx	23/29 (79%)	18/20 (90%)	4/9 (44%)	30/45 (67%)	1/7	0/1
TOTAL	104/137 (76%)*	44/48 (92%)*	11/22 (50%)†	49/73 (67%)†	1/7 (14%)‡	3/8 (38%)‡

NA, no data available.
* $P = .02$
† $P = .11$
‡ $P = .34$
Note: University of Florida data; analysis March 1991.

TABLE 12-16. Twice-a-Day Irradiation of the Head and Neck: Complications of Irradiation (419 Patients)

Complication	Mild	Moderate	Severe
Necrosis			
Soft tissue	20	3	1
Cartilage	0	0	5
Bone	8	3	5
Esophageal stricture	0	0	1
Severe laryngeal fibrosis*	NA	NA	3
Permanent gastrostomy†	NA	NA	3
TOTAL			18 (4%)

NA, no data available.

* Tracheotomy required for airway obstruction (two); arytenoidectomy (one).

† For swallowing dysfunction (motility versus stricture). Two of three occurred in patients with pharyngeal wall cancer.

Note: University of Florida data. Patients treated March 1978 to March 1989; analysis March 1991.

to 30 percentage points in local control in the twice-a-day groups. For T2, T3, and T4 lesions of the oropharynx, the results were essentially the same.

Complications of irradiation are shown in Table 12-16. There was a 4% rate of severe complications.

The incidence of severe complications by site and T stage for 217 patients with laryngeal and hypopharyngeal cancers is shown in Table 12-17. The rate of severe injury was 6%. There were two severe injuries in 85 patients (2%) with T1 and T2 cancers. The incidence was 6% for T3 and 20% for T4 cancers. Twelve of 13 severe complications occurred in patients who would have required total laryngectomy had they been treated surgically. The risk of complications was dose-related (Table 12-18). Severe complications occurred in none of 99 patients who received 7440 cGy versus 10% of patients who received 7680 cGy and 17% of those treated to 7920 or 8160 cGy. Patients who received doses of 7920 to 8160 cGy were generally those with T4 cancers who were medically unsuitable for or refused laryngectomy.

Tables 12-19 and 12-20 are similar comparisons for oropharyngeal cancers. The rate of severe complications was 2%. None of 97 patients who received 7440 or 7680 cGy developed a severe complication versus 4% of patients who received 7920 or 8160 cGy or whose treatment included an implant.

No patient developed radiation myelitis.

One hundred two patients underwent a planned unilateral functional or radical neck dissection, usually 4 to 6 weeks after irradiation. Ninety-eight (96%) of the patients received a minimum tumor dose of 7440 cGy or more to the primary site (and thus to the upper neck). Because cobalt-60 was the irradiation source most often used, because the portals were often differentially weighted to the involved side, and because the dose was usually specified at the 90% to 95% of maximum isodose line, the doses to the subcutaneous tissues in the neck were generally in the range of 7800 to 8500 cGy. Despite the fact that the more advanced presentations of disease within each neck substage were usually selected for treatment by irradiation plus neck dissection, the rates of neck disease control were higher than after high-dose irradiation alone (Fig. 12-15), and the operative and postoperative morbidity was acceptable. Wound separations or infections occurred in seven patients (7%); four separations closed spontaneously, two required split-thickness skin graft for closure, and one abscess required incision and drainage. Three patients with advanced neck disease invading the skin required pectoralis major flaps to reconstruct the surgical defects. Flap necrosis occurred in two of the three patients, necessitating deltopectoral flap repair. One additional patient developed a chyle fistula. The overall rate of complications was 10 of 102, or 10%. The median time to hospital discharge after neck dissection was 5 days (mean, 7.5 days; range, 3 to 35 days). There were no carotid ruptures and no fatal complications of neck dissection. The rate of development of distant metastasis in patients whose disease was controlled above the clavicles is shown in Figure 12-16. The rates are substantially higher for patients with stage IVA (T1–3, N2AB–3A) and IVB (T4 or N3B or both) disease than stage II or III disease.

The rate of control above the clavicles according to AJCC stage is shown in Figure 12-17. The control rates for stages III and IVA are the same. Figure 12-18 shows relapse-free survival by AJCC stage, and Figure 12-19 shows absolute survival.

TABLE 12-17. Laryngeal and Hypopharyngeal Cancers: Twice-a-Day Irradiation—Severe Complications According to T Stage

Stage	Supraglottic	Vocal Cord	Pharyngeal Wall	Pyriform Sinus	Total	
T1	0/2	NA	0/3	NA	0/5	(2%)
T2	1/24	0/30	0/13	1/13	2/80	
T3	2/59 (2%)*	2/32 (6%)	3/17 (18%)	0/4	7/112	(6%)
T4	1/2	2/8	1/6*	0/4	4/20	(20%)
TOTAL					13/217	(6%)

NA, no data available.

* Severe complications: two fatal necroses, four total laryngectomies, two tracheotomies, two gastrostomies, one cervical esophageal stricture, one arytenoidectomy for fibrosis, one peridural abscess of cervical spine.

Note: University of Florida data. Patients treated March 1978 to March 1989; analysis March 1991.

TABLE 12-18. Hypopharyngeal and Laryngeal Cancer: Twice-a-Day Radiation Therapy Complications According to Dose (217 Lesions)

Dose (cGy)	Patients	Complications			
		Mild	Moderate	Severe*	
≤7440	99	0	1	0	
7560	1	0	0	0	
7680	99	3	1	10	(10%)
7800–7920	13	0	0	2	(17%)
8160	5	0	0	1	

* Severe complicotions:
Bone necrosis—cervicol spine (peridurol obscess ofter 7680 cGy)
Cartilage necrosis—two T3, three T4 (four at 7680 cGy; one fatal at 8160 cGy)
Soft tissue necrosis—one T3 (fatal at 7680 cGy)
Esophogeal stricture—one (at 7680 cGy)
Permonent gostrostomy—two (ot 7920 cGy; both T3 tumors of posterior phoryngeol wall)
Loryngeal fibrosis producing airway obstruction or aspirotion:
Permanent tracheostomy—one T3, one T4 (both at 7680 cGy)
Arytenoidectomy—one T2 pyriform sinus (at 7680 cGy)
Note: University of Florida dota. Patients treoted March 1978 to Morch 1989; anolysis March 1991.

TABLE 12-19. Oropharyngeal Cancers: Twice-a-Day Radiation Therapy—Severe Complications According to T Stage

Stage	Tonsil	Base of Tongue	Soft Palate	Total*
T1	0/9	0/5	NA	0/14
T2	1/37	0/16	0/12	1/65 (2%)
T3	2/46	1/23	0/13	3/82 (4%)
T4	0/19	0/13	0/1	0/33
Total				4/194 (2%)

NA, no data available.
Three bone necroses, one gastrostomy.
Note: University of Florido data. Potients treated March 1978 to March 1989; analysis March 1991.

CONCLUSIONS. Conclusions regarding the University of Florida experience with twice-a-day irradiation of cancers of the oropharynx, hypopharynx, and larynx are as follows:

1. Acute mucosal reactions were more severe than observed with 180 to 200 cGy given once a day. However, doses of 7440 to 8160 cGy at 120 cGy twice a day can be administered in 6 to 7 weeks without a split in the treatment course. About 15% of patients developed severe problems with alimentation, and all patients require special attention to nutritional status.
2. Local control results after twice-a-day irradiation were equal to or better than after once-a-day treatment for all subgroups (T2, T3, and T4 tumors of the larynx, hypopharynx, and oropharynx). No dose–response relation was apparent for local control in the rather narrow range of doses employed (7440 to 8160 cGy).
3. The risk of severe complications correlated with dose and T stage. The oropharynx tolerated generally higher doses than the larynx or hypopharynx. An interstitial boost implant (limited to the area of heaviest tumor infestation) was tolerable.
4. Planned neck dissection 6 weeks after irradiation significantly improved neck control rates for N2A–3A and N2B–3B disease compared with irradiation alone and was accomplished with acceptable morbidity.

Randomized Trials

The first randomized trial of pure hyperfractionation was EORTC trial 22791. From January 1980 to April 1987, 356 patients were accrued to compare 7000 cGy in 35 fractions of 200 cGy over 7 weeks with 8050 cGy in 70 fractions of 115 cGy administered twice a day (4- to 6-hour interfraction interval), also delivered in 7 weeks. The trial included patients with oropharyngeal cancers (excluding those arising in the base of tongue) with stages T2–3 N0–1. The 5-year local control rate was significantly higher in the twice-a-day group (59% versus 40%; $P = .02$). The improvement in local-regional control resulted in an improved rate of survival ($P = .08$). The

TABLE 12-20. Oropharyngeal Cancers: Twice-a-Day Radiation Therapy—Complications According to Dose (194 Lesions)

Dose (cGy)	Patients	Complications			
		Mild	Moderate	Severe*	
≤7440	46	1	0	0	
7560	2	0	0	0	0/99
7680	49	6	1	0	
7800	2	0	0	0	
7920	29	3	1	2	
8160	12	2	1	0	4/95 (4%)
7440–8160 + 1000–1500cGy (implant)	54	11	2	2	

* Severe complications: permanent gastrostomy, one (7920 cGy); bone necrosis, three (7920 cGy; two at 7680 cGy plus implant)
Note: University of Florida data. Patients treated March 1978 to March 1989; onolysis March 1991.

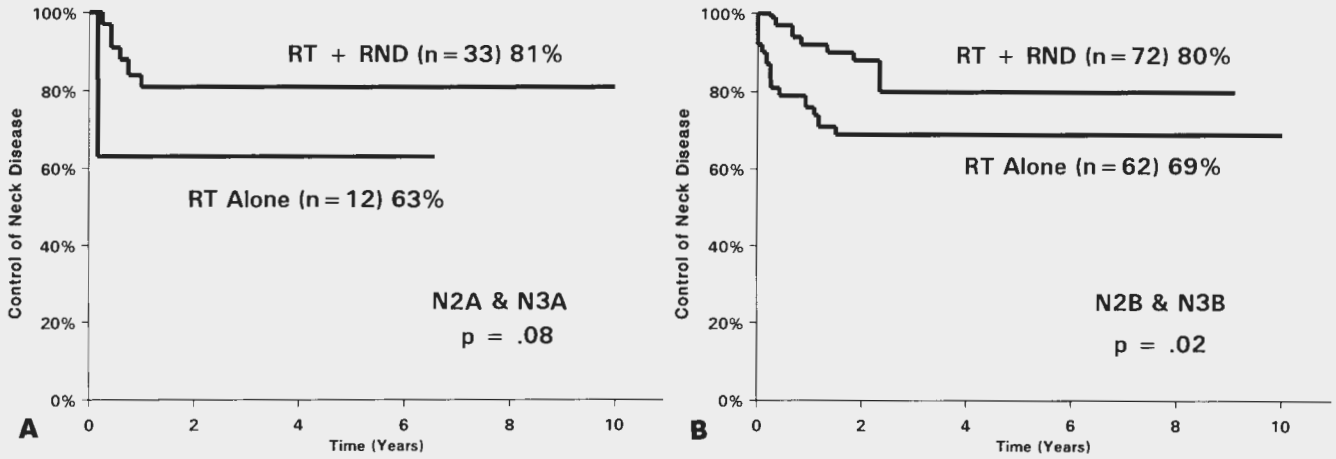

Figure 12-15. Probability of control of neck node metastases after twice-a-day irradiation alone or twice-a-day irradiation followed by planned neck dissection. University of Florida data; patients treated March 1978 to March 1989; analysis March 1991. (*A*) N2A–3A. (*B*) N2B–3B.

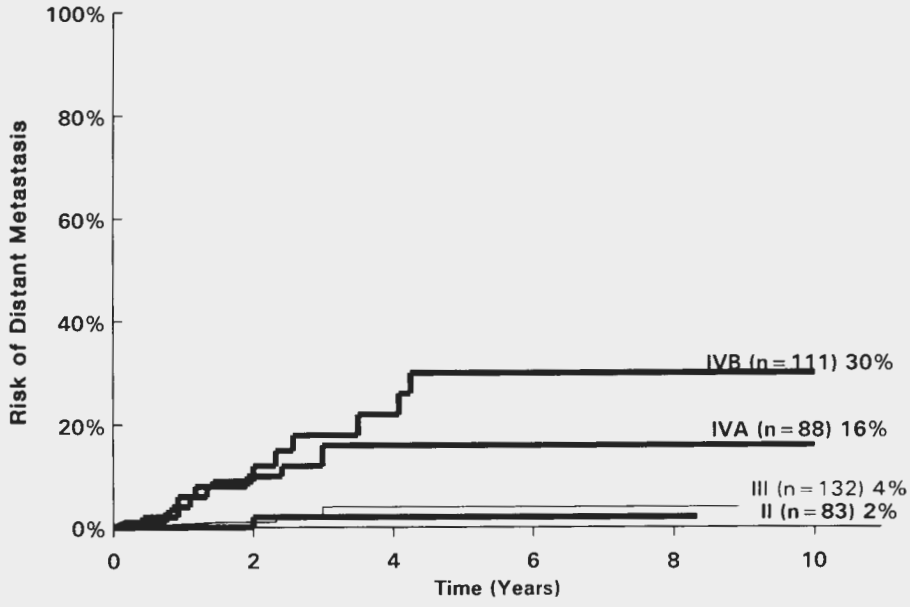

Figure 12-16. Risk of developing distant metastasis in patients whose disease was controlled above the clavicles after twice-a-day irradiation. University of Florida data; patients treated March 1978 to March 1989; analysis March 1991.

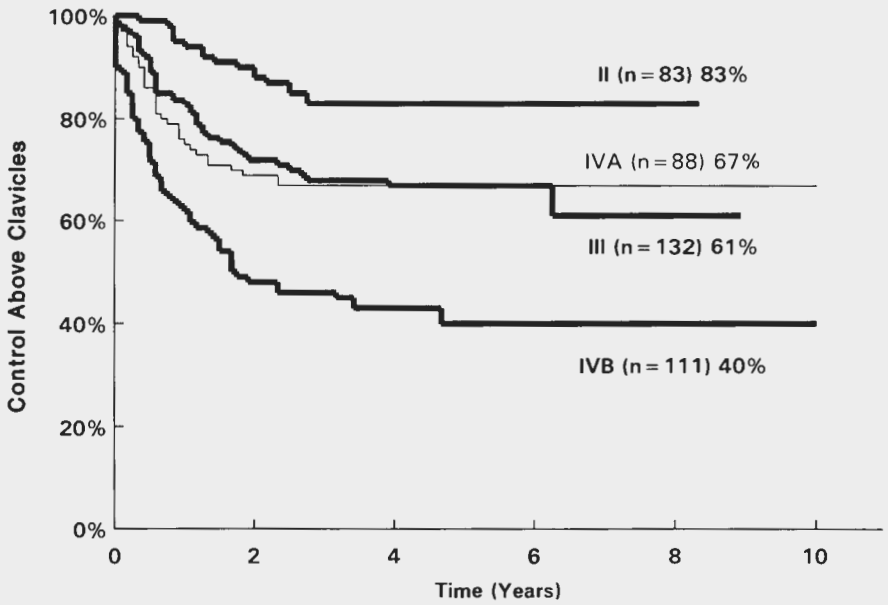

Figure 12-17. Control above the clavicles after initial treatment with twice-a-day irradiation with or without radical neck dissection. Patients who underwent successful salvage surgery are scored as failures. University of Florida data; patients treated March 1978 to March 1989; analysis March 1991.

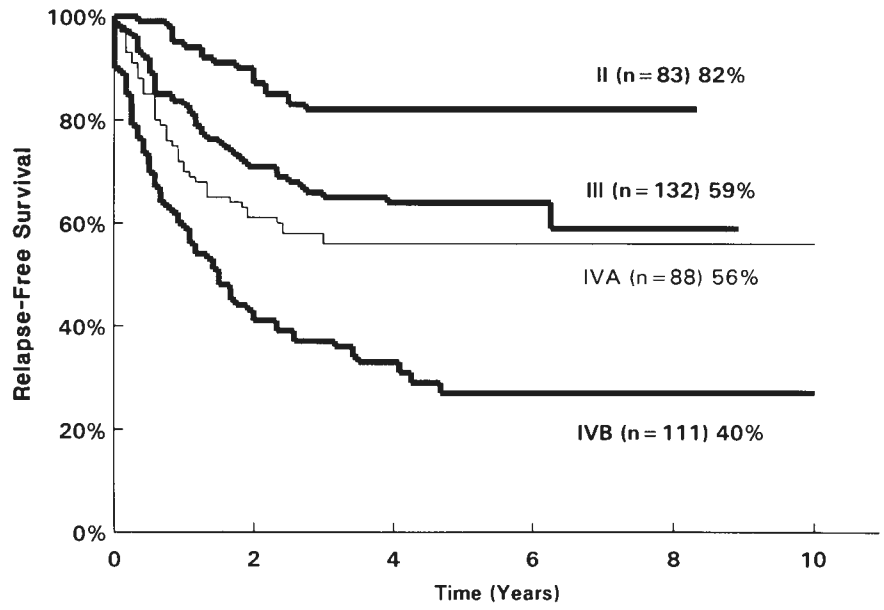

Figure 12-18. Relapse-free survival after treatment with twice-a-day irradiation. University of Florida data; patients treated March 1978 to March 1989; analysis March 1991.

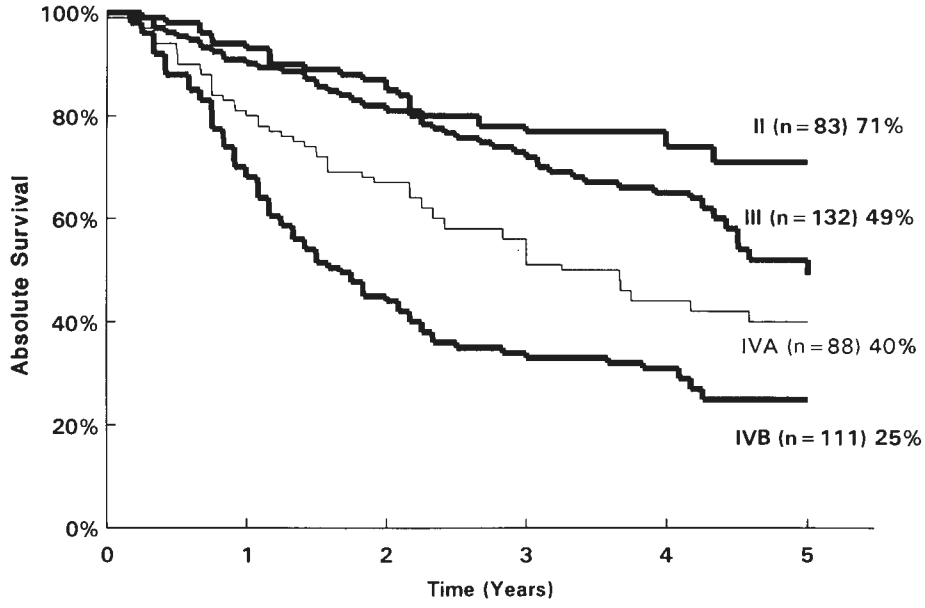

Figure 12-19. Absolute survival after treatment with twice-a-day irradiation. University of Florida data; patients treated March 1978 to March 1989; analysis March 1991.

largest improvement in tumor control was observed in patients with high performance status (Karnofsky 90 to 100). Acute mobility was more severe in the twice-a-day group ($P = .02$). There was no difference in late normal tissue damage.[81]

Datta and coworkers[32] randomly assigned 212 patients with previously untreated T2–3 N0–1 cancers of the oral cavity, oropharynx, or larynx to receive external-beam irradiation consisting of 6600 cGy in 33 fractions of 200 cGy each over 6½ weeks versus 7920 cGy in 66 fractions of 120 cGy administered twice a day (4- to 6-hour interfraction interval), also over 6½ weeks. The spinal cord was excluded after 4800 cGy. All patients had 2 years' minimum follow-up. Acute reactions were more pronounced in the twice-a-day group. Late reactions were thought to be equivalent. No radiation myelitis was observed. Disease-free survival at 2 years was significantly higher in the twice-a-day group (63% versus 33%, $P < .001$). The 2-year absolute survival rate was also significantly higher in the twice-a-day group (71% versus 45%, $P < .005$).

From August 1979 to June 1983, the RTOG conducted a randomized trial on stage II, III, and IV tumors of a variety of head and neck sites comparing 6600 to 7400 cGy in 33 to 41 fractions of 180 to 200 cGy administered once a day (5 days per week) over 6½ to 8 weeks with 6000 cGy in 50 fractions of 120 cGy administered twice a day (3- to 6-hour interfraction interval) over 5 weeks.[103] Acute reactions were more severe in the twice-a-day group; 36% of the twice-a-day patients required splits in the treatment course (a much higher percentage than anticipated from the University of Florida experience in which, despite higher total doses, unplanned splits occurred in 1%). Late reactions were equal in the two

groups. In the twice-a-day group, both acute and late effects were more pronounced in patients whose interval between fractions was less than 4½ hours. Despite significantly lower total doses (by 600 to 1400 cGy) in the twice-a-day group, the local–regional control results were equivalent in the two groups.

Between 1983 and 1987, the RTOG conducted a trial of 479 patients with squamous cell carcinoma arising from a variety of sites in the head and neck. All three groups were administered 120 cGy twice daily, 5 days per week, with 4 to 8 hours between fractions. Patients were randomized to total doses of 6720, 7200, or 7680 cGy. After acceptable toxicity was observed in the group receiving 7680 cGy, a fourth group of patients receiving 8160 cGy was studied, and study of the group receiving 6720 cGy was closed. Two-year local–regional control rates were 25% after 6720 cGy compared with 43% to 45% for the other three groups. Survival rates did not differ significantly among the four groups. For each group, the incidence of grade 4 (severe) late effects was higher in patients whose average interval between fractions was less than or equal to 4½ hours. Actuarial estimates of the incidences of grade 4 late toxicity for the 197 patients for whom the average interval between fractions was less than or equal to 4½ hours were 5.5% at 1 year, 8.8% at 2 years, and 15.4% at 3 years. Estimates of grade 4 toxicity when the intervals were more than 4½ hours were 1.7% at 1, 2, and 3 years (P = .006). There were no significant differences in severe late effects among the different levels of total dose (5% to 9% for the four dose levels treated with less than or equal to 4½-hour intervals versus 0% to 3% for patients whose fractions were given at more than 4½-hour intervals).[31]

Accelerated Fractionation

By definition, *accelerated fractionation* refers to shortening the overall treatment duration, using conventional dose fractions (eg, 180 to 200 cGy). The total dose is usually similar to or less than that conventionally used. The rationale for acceleration is to limit the extent to which tumor cell regeneration occurs during a course of treatment. Since no regeneration of late-reacting tissues would be expected over the treatment course, a reduction in overall treatment time should not increase the severity of late effects, provided that there is sufficient time between fractions to allow complete repair of sublethal damage. Acute mucosal reactions limit the extent to which treatment can be accelerated. Accelerated treatment would be most appropriate in tumors that are rapidly proliferative or that have a high regenerative potential. In practice, it is possible to accelerate treatment by several methods. *Accelerated once-a-day fractionation* schemes deliver treatment once a day for 6 or 7 days per week, instead of the usual 5. This technique has received little attention in the United States.[95]

Short-course intensive accelerated fractionation markedly reduces the overall treatment duration (eg, by administering 150 to 200 cGy three times a day) in a continuous course of irradiation administered over 1½ to 2 weeks. Total doses are limited by acute reactions to 5000 to 5400 cGy.[69,140,146,152] Many of the patients require hospitalization in the postirradiation period until the peak of the reaction has passed, and, in some of the reported series, patients have died in the postirradiation period of treatment-related complications. Because the total dose is substantially reduced, such schedules may also be disadvantageous in terms of tumor control compared with schedules in which the total dose is not compromised.[142]

In 1989, Dische and Saunders[38] reported the unexpected occurrence of two cases of radiation myelitis in patients whose spinal cords received 4200 and 4360 cGy (150 cGy three times a day with 6-hour interfraction intervals), respectively, before portal reductions that excluded the cord.

Accelerated split-course fractionation schemes deliver multiple fractions per day to conventional total doses, made possible by the introduction of a rest interval to alleviate severe acute reactions. The overall treatment time is only modestly reduced compared with conventional-course fractionation.

In an important demonstration of the effect of overall treatment time, Wang and associates[189] showed that a dose of 6400 to 6720 cGy (160 cGy twice a day with a 2-week split) given in an overall treatment time 1 to 2 weeks shorter than that used to administer the same total dose once a day resulted in significantly improved tumor control.[138]

Concomitant boost accelerated fractionation, described by Knee and associates,[88] is a variant of accelerated fractionation in which the basic treatment course (180 to 200 cGy per fraction) and the boost course (120 to 150 cGy per fraction given 3 to 6 hours after the basic dose, two to three times per week) were administered concomitantly to 53 patients with advanced, recurrent, or rapidly progressive squamous cell carcinoma of a variety of head and neck sites.[88] The duration of treatment is reduced by the time usually taken to give the boost (1½ to 2 weeks). The rationale is the same as for accelerated fractionation in general, but the regimen has the advantage of producing the most severe mucosal reactions in a limited volume of tissues because only the boost field is treated at an accelerated rate.

Based on encouraging preliminary results, a randomized study to compare three different boost techniques in patients with T2–3 carcinomas of the oropharynx and nasopharynx was undertaken. All three groups in the study received a basic dose of 30 fractions of 180 cGy each to a total of 5400 cGy. The boost was administered during the first 2 weeks or the last 2 weeks or was evenly spread throughout the treatment course and consisted of 1500 to 1800 cGy in 10 to 12 fractions, thus bringing the total dose to 6900 to 7200 cGy in 6 weeks. Potential advantages seem to weigh in favor of delivering the boost during the last 2 weeks, which has the greatest probability of allowing delivery of the full dose without treatment interruption. Moreover, since the regenerative response of the mucous membranes is already in full swing at the time of the boost, tolerance should be improved relative to the other regimens.[142] Preliminary analysis suggests slightly higher primary control rates (P = .11) in patients whose boosts were administered during the last 2 to 2½ weeks of treatment.[5]

Other Fractionation Schemes Utilizing Multiple Fractions per Day

A number of other nonstandard schemes of fractionation defy neat categorization into hyperfractionation or accelerated fractionation, as defined earlier. There are an infinite number of possible schedules, some of which have no clear-cut radiobiologic rationale.

EORTC protocol 22811 compared 7000 cGy in 35 fractions over 7 weeks to 4800 cGy over 2 weeks using 160 cGy three times a day, followed by a 4-week rest, followed by 2400 cGy using the same fractionation (overall treatment time, 6 to 8 weeks). The technique had some elements of hyperfractionation (slight decrease in fraction size, same total dose and overall treatment time). Although each portion of the program was itself accelerated, the rest interval was of such length that there was no acceleration of the overall treatment time. Conclusions based on 523 patients were that 4800 cGy over 2 weeks was at the upper limit of acute tolerance and often produced such severe mucositis that patients were unable to restart radiation therapy until after more than 4 weeks' rest. The result was no improvement in local control.[81] This experience led to EORTC trial 22851, in which the intensity of the first phase of therapy is reduced so that the second phase can be initiated within 2 weeks, resulting in pure acceleration (7200 cGy over 5 weeks). The peak reaction occurs after, rather than during, therapy. The trial was activated in December 1985.[81]

Nguyen and associates[127] observed unacceptable acute toxicity (extensive mucosal necrosis, hemorrhage, fatalities, and severe edema) after 7200 cGy over 3½ weeks administered as 90 cGy per fraction, eight fractions per day (2 hours between treatments) for 5 days, a 2-week split, and then a repeat of the same dosage schedule. Few patients survived 2 years, but most who did suffered from necrosis, severe laryngeal edema, trismus, and cervical fibrosis. Probably several factors account for the problems. Such excessive rates of dose accumulation lead to total or near-total epithelial denudation such that healing, if it occurs, must occur by migration of surviving epithelial stem cells from the periphery of the injured area. Total loss of mucosal integrity may lead to so-called acute necrosis or consequential late necrosis. These latter terms describe injury to a late-responding tissue that is the direct consequence of an extremely severe acute injury. Although it is often observed that there is a dissociation between acute and late effects, the two may be directly related at this extreme rate of dose delivery.[142] An additional contributing factor was the inadequacy of the 2-hour interfraction interval.[127]

Some techniques offer no apparent radiobiologic advantage, whereas others combine most of the features that would be considered disadvantageous (eg, two large-dose fractions per day to a low total dose given in a conventional overall treatment time with a long split in the treatment course).[128]

Summary of Time–Dose Recommendations for External-Beam Treatment of Primary Lesions

Repopulation kinetics change during treatment. Accelerated repopulation is believed to be a potent cause of treatment failure. Accelerated growth involves small numbers of tumor clonogens and, rather than being detectable clinically as tumor growth, occurs while the mass is regressing.[197] Once treatment is begun, it should be completed as quickly as possible to limit the effects of tumor repopulation during treatment. Acute responses become the limiting factor. Extremely abbreviated schedules have the theoretical disadvantage of not allowing adequate time for reoxygenation to occur during treatment. If treatment delays can be predicted (eg, holidays, machine maintenance), it is probably advisable to delay the start of treatment by several days rather than interrupt treatment once it has begun since the consequences of delaying treatment (when the clonogen doubling time is about 60 days) are less than the influence of interrupting therapy (when the clonogen doubling time may have shortened to 4 days). If treatment is scheduled to finish on a Monday or Tuesday, it may be possible to treat the patient six or seven times the week before treatment is completed (eg, with 6 to 8 hours between fractions on 1 or 2 days) so that treatment is completed on a Friday.

There are a variety of schedules that allow one to shorten the overall treatment duration. With the exception of vocal cord cancer, for which small fields (4.5 to 5 cm × 4.5 to 5.5 cm) have been safely (less than 1% risk of severe necrosis or edema) treated for many years to doses of about 6300 cGy in 28 fractions over 5½ weeks, it is generally not recommended to deliver full-dose external-beam treatment with dose fractions that exceed 200 cGy per fraction. The overall treatment duration using hyperfractionated therapy at the University of Florida is 1½ to 2 weeks less than it was in the past using once-a-day schedules at 180 cGy/d.

For patients with suitably located lesions (oral tongue, floor of mouth, anterior tonsillar pillar, or soft palate) it is sometimes possible to shorten the treatment duration by using an intraoral cone (eg, by initiating treatment with 1500 to 2000 cGy in five to eight fractions). Although the dose per fraction is large, such therapy has proved tolerable because the treatment volume is limited by the small size of the treatment cone and because the depth doses are relatively low owing to short treatment distances (when orthovoltage x-rays are used) or dose fall-off (when electrons are used). Overall treatment duration can also be limited by administering a portion of the dose with interstitial therapy. For example, T2 oral tongue cancer that is treated by irradiation at the University of Florida commonly receives 3000 cGy in 10 fractions over 2 weeks followed a few days later by an interstitial implant (3500 to 4000 cGy over 3½ to 4 days) so that the entire treatment course is complete within 3 weeks.

Total dose and dose per fraction are decided at the outset. Unplanned treatment interruptions are largely avoidable by using portals that do not excessively irradiate mucosal surfaces that are at little or no risk of involvement, by using field reduction techniques, and by ensuring adequate nutritional support during treatment (dietary consultation, adequate analgesia, and feeding by nasogastric or gastrostomy tube if necessary). The philosophy of starting aggressively, then seeing how much dose can be delivered before the patient requires a treatment break or breaks, should be an approach of the past. Unfortunately, the approach is still widespread.

DOSE-RATE EFFECTS

Interstitial Implantation: Continuous Low-Dose-Rate Irradiation

Continuous low-dose-rate irradiation may be likened to fractionated irradiation with an infinite number of small individual doses. The continuous low-dose-rate tech-

nique is commonly used in head and neck cancer therapy since this is the method of dose delivery by interstitial implants. There is little experience with continuous low-dose-rate irradiation by external beam.[145] The dose-rate effect is illustrated in Figure 12-20.[70] Continuous low-dose-rate and multiple daily fractionation schemes presumably share the same potential radiobiologic advantages. Experimental data suggest that cells exposed to continuous low-dose-rate irradiation tend to accumulate or pile up in the G2 to M (sensitive) phase of the cell cycle.[86]

Advantages and Disadvantages of Interstitial Implantation

When supervoltage equipment became widely available, interest in interstitial treatment declined in many centers. There are still situations for which interstitial implantation, alone or combined with external irradiation, is more appropriate than external irradiation alone.[22] For lesions of the oral tongue or floor of mouth it is essential to use either interstitial treatment or an intraoral cone when irradiation is used. Implants deliver a high dose in a short time (eg, 6000 to 6500 cGy in 6 to 8 days as opposed to 6 to 7 weeks of external therapy) to a limited volume of tissue with rapid decrease in dose outside the implant volume. For some small tumors, implantation alone is sufficient. In other situations, the implant is used after external-beam treatment to boost the dose to the bulky central portion of the tumor, thereby limiting the high-dose volume. In still other circumstances, the implant is the main treatment, but moderate-dose external irradiation (3000 cGy over 2 weeks) is given before the implant to compensate for areas of localized underdosage ("cold spots") within the implanted volume, to flatten the tumor (eg, for bulky lip cancer) so as to improve the implant geometry, or to irradiate the lymph nodes electively (eg, for oral tongue carcinoma). Interstitial irradiation has some potential disadvantages:

1. The dose throughout the implanted volume is inhomogeneous. Areas of localized underdosage (cold spots) may result in local recurrence. Conversely, bunching of sources may produce areas of overdosage (hot spots) that cause necrosis.
2. Technical and conceptual skills are required to achieve a good dose distribution. Some problems of achieving good geometry are overcome by using preloaded implant devices[41,104] or afterloading techniques, but a textbook-like distribution is not possible every time. On the other hand, Martin and Martin,[106] who had vast experience with radium implantation, noted that some deviation from perfect was acceptable, as long as the overall pattern of the implant covered the desired volume. Slight variations seemed to make little difference in their treatment results, and the University of Florida experience is in agreement: the most perfect-appearing implant may be unsuccessful, whereas the one that looks geometrically poor may control the cancer.
3. Hospital admission is required. General anesthesia is usually necessary, and tracheostomy is necessary in some situations.
4. Therapists and operating room personnel are exposed to radiation. Although the problem of exposure cannot be entirely eliminated, it can be reduced by using either preloaded implant devices that can be rapidly positioned[41,104] or afterloading techniques. Compared with a typical gynecologic radium case, in which 65 mg or more of radium is loaded into a tandem and ovoid system, only 8 to 10 mg of radium is used in a typical head and neck implant case, and therefore personnel exposure is relatively low.

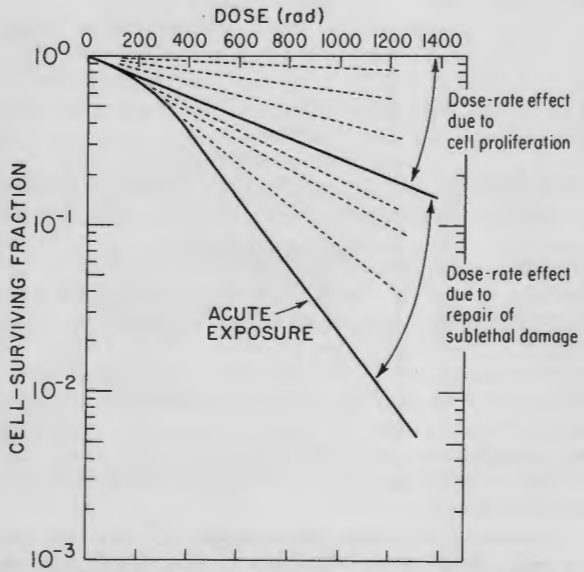

Figure 12-20. Dose-rate effects due to repair of sublethal damage and cell proliferation. The lower solid line illustrates the dose–response curve for cells following a single x-ray exposure. Note the broad initial shoulder on the curve. As the dose rate (ie, cGy [rad] per hour) is reduced (*lower dotted lines*), repair of sublethal damage may take place during the exposure. If the dose rate is low enough, all sublethal damage is repaired and the survival curve assumes the shape of the upper solid line, with all damage being due to single hits. If the dose rate is sufficiently low (*upper dotted lines*), a critical level may be reached where cell proliferation continues during the radiation exposure. At the dose rates (30 to 100 cGy/hr) generally used clinically in low-dose rate continuous therapy, a dose-rate effect due to cell proliferation is probably not very important. (Hall EJ. Radiobiology for the radiologist, ed 2. Hagerstown, MD, Harper & Row, 1978: 146)

The relative disadvantages of implant therapy can generally be overcome by careful planning. It is difficult to compare doses between patients treated by external-beam, interstitial, or both types of irradiation, since dose distributions and times over which the dose is administered differ greatly for the various techniques. Although it may be argued that mere addition of the external and interstitial doses is inappropriate, such additions must be performed almost routinely in the clinic whenever one combines external-beam and interstitial irradiation; it therefore makes some sense to combine the doses when reviewing the data. The University of Florida data on T2 oral tongue carcinoma suggest that the greater the proportion of the total dose given by radium as opposed to external beam, the higher is the rate of local control[119,120]: 12 of 16 (75%) for interstitial implant plus less than or equal to 3000 cGy from external-beam irradia-

tion versus 6 of 15 (40%) for interstitial implant of 2000 to 3000 cGy plus more than 3000 cGy from external beam (P = .05). (See Figure 16-46 in Chapter 16.) Local control was significantly better (P = .012) for patients who were treated in 40 days or less (14 of 18, 78%) compared with those whose overall treatment time was more than 40 days (4 of 13, 31%), despite the fact that the total doses were higher in the latter group. (See Figure 16-47 in Chapter 16.) Local control was achieved in only 3 of 7 patients who received a total dose of 8000 cGy or more in overall treatment times that exceeded 40 days.

Martin and Martin[106] observed that oral tongue lesions "responded quite well" to treatment with 6000 R over 7 days from a radium implant, but 7000 R over 5 to 7 weeks from a "cobalt bomb" was generally incapable of producing cure. In an analysis of 55 patients with T1–2N0 oral tongue cancer treated at the M.D. Anderson Hospital between 1970 and 1979, Wendt and coworkers[192] noted a 5-year probability of local control of 90% for those who received more than 3000 cGy of interstitial therapy versus 65% for those whose interstitial dose was less than 3000 cGy (P = .04). Several others have also published data showing improved local control for cancer of the oral tongue and floor of the mouth treated by implant alone or implant plus external-beam irradiation versus external-beam irradiation alone.[30,61,62,82,84,93,120] There are some differences when considering individual T stages, and the reader is urged to individually review the cited papers.

Dose Specification

Dosimetry for all except the simplest implants is done by computer. At various points within the implanted volume, the doses contributed by each radioactive source are summed; points of equal dose are then connected by lines, called isodose lines. Isodose lines through several levels of the tumor should be reviewed, and at least two planes of calculation, generally at right angles to each other, should be viewed. The tumor volume is drawn onto each isodose plot using both knowledge of the anatomic distribution of tumor as well as the known relation of each radioactive source to the tumor. Although computer dosimetry provides a large amount of dose information, including information regarding "hot" and "cold" areas that would not be readily available with conventional methods of calculation, there is still the problem of where to specify the dose. In the early years of computer dosimetry, the tendency was to be overgenerous in selecting minimum tumor doses, often resulting in higher doses to larger volumes than had previously been given when calculations were made by the Paterson-Parker method. At M.D. Anderson Hospital, where computer dosimetry became available in January 1961, overdosage led to low recurrence rates (3 of 30, or 10%) in lesions of the oral tongue and floor of the mouth treated in 1961 to 1962, but 77% of the patients developed soft tissue necrosis and 13% required surgical treatment of bone necrosis.[29]

No general rule can be stated regarding the choice of the isodose line with which one specifies the minimum tumor dose. The rapid change in dose surrounding an implant makes dose specification somewhat arbitrary. Comparisons of interstitial dose between two institutions may be meaningless, since the technique of dose specification varies from center to center; indeed, the selection may vary within a single institution by a single physician. At the University of Florida, an isodose line 3 to 5 mm outside a two-plane implant and about 5 mm from a single-plane implant is usually chosen. In volume implants such as those used in treating nasal vestibule cancer, the minimum isodose line that covers the area of gross disease plus a margin of a few millimeters is usually selected. However, depending on the physician's clinical judgment (ie, whether he or she thinks a tumor will be difficult or easy to control), there is always a "fudge factor" whereby a little higher or lower total dose than usual may be administered by merely selecting a slightly more or less generous isodose line. For both cases, the tumor dose that is said to have been delivered would be identical even though the actual doses might differ by 10% to 15% or more. Judgment must be used in each case. As an example, the 40- and 70- or 80-cGy/h lines may be only millimeters apart. If one selects the 40-cGy/h line, the dose to much of the implanted volume will be twice the specified dose. Generally, the isodose lines for each decade between 10 and 100 cGy/h are displayed and examined. If it is necessary to show other isodose lines, these, too, are displayed. The technique routinely adopted by Martin and Martin[106] of leaving a full-intensity implant in place for 7 days can hardly be criticized considering their good results and the lack of consistency in today's methods of dose specification. The Paris system of dosimetry for iridium implants probably represents the best effort to date to standardize the means of dose specification.[39] The technique has not been used at the University of Florida.

Paterson[139] and Ellis[42] both recommended adjustment of the total interstitial dose according to dose rate. Paterson used as his reference a 7-day implant and set out the doses that, when given in 5 to 10 days, would be equivalent to the 7-day dose. As an example, suppose one desired an effect equivalent to 6000 cGy over 7 days (36 cGy/h). If the geometric arrangement of sources was such that a higher dose rate (eg, 46 cGy/h) was achieved, then according to Paterson's recommendations the total dose should be reduced to about 5500 cGy over 5 days. Conversely, if a dose rate lower than 36 cGy/h was obtained, then a total dose higher than 6000 cGy should be administered in an overall time of greater than 7 days. The initial Paterson curve owed more to inspiration than to science but was said to have been gradually corrected over a period of time to match his actual experience. Since no data were ever published to substantiate either the Ellis or Paterson curves, one cannot assess their degree of accuracy.

The data of Pierquin and associates[144] on interstitial treatment of cancer of the floor of the mouth and oral tongue indicate that for the same tumor dose of 7000 cGy, the treatment time may vary from 3 days (approximately 90 cGy/h) to 9 days (approximately 30 cGy/h) without affecting the rates of necrosis or tumor recurrence. For 3- to 9-day treatments, Pierquin and coworkers concluded that one need not adjust the total dose to compensate for different dose rates. The authors reached the same conclusion in a reanalysis of their data in 1990.[108] Awwad and coworkers,[9] in treating T1–2 tongue cancers by interstitial radium, usually adjusted the total dose according to dose rate so that supposedly biologically equivalent doses would be achieved. When the total dose was lowered to correct for higher dose rates, local control was poor.

At the University of Florida, no adjustment in total dose is recommended for implant therapy in the range of

30 to 80 cGy/h; implants are usually planned such that the dose rate is 40 to 50 cGy/h, thereby largely eliminating dose rate as a variable. Low-intensity (0.33 to 0.66 mg/cm radium equivalent) sources are chosen. Small-volume implants (eg, T1 cancers of the floor of mouth) usually require 0.66-mg/cm needles, whereas large-volume two- or three-plane implants usually require 0.33-mg/cm needles to achieve the desired dose rate.

At the University of Florida, a dose reduction in interstitial implant therapy is not recommended when treating large tumors. The dose in such cases is, in fact, generally higher. Pierquin's experience with carcinomas of the floor of the mouth and oral tongue justifies this approach.[144] When patients are grouped according to overall treatment time, one notes that as the T stage (and thus implanted volume) increases, there is a trend toward higher rates of necrosis. The increased rate of necrosis is, however, not so great that one should risk underdosage of tumor.

External-Beam Irradiation: Effect of Time per Treatment Session

Turesson and coworkers[180] investigated the effect of extending the length of each individual treatment session on the severity of acute and late reactions in human skin. Patients received irradiation with 12-MeV electrons to bilateral parasternal fields after mastectomy. Two different treatment schedules were used. Each patient served as her own control. Each parasternal field received 790 cGy per fraction, 1 day per week, for a total of four treatments over 22 days. The dose rate was 200 cGy per minute to each side, but the treatment to the left parasternal field was interrupted for 14 minutes twice during each fraction, so that the total dose to the left side was administered over 32 minutes, and the dose to the right was administered in 4 minutes. The prolonged sessions produced significantly less acute erythema ($P < .001$) and telangiectasia at 5 years ($P < .001$). It was estimated that when the individual treatment session was prolonged, the total dose required to produce equivalent acute and late end-points was about 10% higher.

Whether the magnitude of the observed differences would be less with more conventional dose fractions is unknown. The problem might be of clinical importance in patients with complicated setups during which a significant amount of time might elapse before all of the fields to the target volume were treated. The problem might be especially significant in patients whose treatment plan called for treatment on more than one treatment machine (eg, cobalt and electrons) per day. A significant interruption of each treatment session would be likely on many days. In the latter case, it might be preferable to treat the patient on one machine per day (eg, 3 days per week on the accelerator and 2 days per week on the cobalt unit) unless the daily dose distribution would be too inhomogeneous.

PLANNED COMBINED TREATMENT TO THE PRIMARY SITE

Failure of irradiation alone to control large masses is frequent. On the other hand, surgery is good for large, resectable cancers, but even radical procedures frequently fail to remove all microscopic tumor in the presence of extensive infiltration. Planned combined surgery and irradiation is therefore a useful approach for certain large primary tumors in which treatment by a single modality would likely be unsuccessful. Neck dissection is often included. Either preoperative or postoperative irradiation may be employed; each has advantages and disadvantages.

Postoperative Irradiation

Although 5000 cGy in 25 fractions produces a high rate of control of subclinical lymph node disease in surgically undissected sites in the head and neck region, higher doses are required in the postoperative setting because (1) the density of infestation of the tissues by tumor cells is potentially much greater in the latter setting,[52,53] (2) surgical interruption of the normal vasculature and scarring in the tumor bed result in hypoxia, and (3) remaining cancer cells are probably in a rapidly proliferative state. Failure to control cancer above the clavicles continues to be a relatively common problem and appears in part to be dose related. Modest doses (4500 to 5400 cGy over 5 to 5½ weeks) of postoperative irradiation at Memorial Sloan-Kettering Cancer Center resulted in a 50% failure rate above the clavicles in 14 patients with a variety of head and neck primary sites who had at least 2 years of follow-up.[186] At Massachusetts General Hospital, Mirimanoff and coworkers[124] reported failure rates after a median dose of 3750 cGy in 23 fractions that were comparable to those reported by Looser and associates[96] after surgery alone. For patients with negative margins, Mirimanoff and coworkers reported a 29% failure rate versus 32% reported by Looser and associates; for positive margins, Mirimanoff and coworkers reported a 65% failure rate versus 71% by Looser and associates after surgery alone.

Tumor Control According to Primary Site

Most reports show higher failure rates after postoperative irradiation of oropharyngeal or oral cavity cancers than for tumors of the larynx and hypopharynx. In a prospective randomized RTOG study, the 4-year local–regional control rate after postoperative irradiation was 44% for oral cavity, versus 61% and 77% for hypopharynx and supraglottic larynx, respectively.[90] At the M.D. Anderson Hospital, control rates above the clavicles after laryngectomy and postoperative irradiation for supraglottic larynx and pyriform sinus cancers were 87% and 89%, respectively,[54,66] versus 49% (19 of 39) in patients who received 5000 to 6000 cGy for advanced cancers of the oral cavity or oropharynx.[72] Updated results from the M.D. Anderson Hospital and Memorial Sloan-Kettering Cancer Center for oral cavity and oropharyngeal cancers showed failure rates of about 40% at both institutions. Feldman and Fletcher[46] reported on 81 patients with 2 years' minimum follow-up. Postoperative doses were 6000 to 6500 cGy in 75% (61 patients) and 5000 to 5500 cGy in the remainder. Thirty-one patients (38%) developed in-field (dose-related) failure above the clavicles. When surgical margins at the primary site were positive, doses in the range of 6000 to 6600 cGy controlled the primary lesion in only three of nine patients; in several patients, the dose to the site of failure was less than spec-

ified because failure occurred near the field edge. In the Memorial Sloan-Kettering series, when patients who died of intercurrent disease or distant metastatic cancer (with continuous control of disease above the clavicles) were excluded from analysis, failure was noted in 14 (40%) of 35 patients after 4500 cGy over 4½ weeks to 6000 cGy over 6 weeks.[187]

At Stanford University, 14 patients received composite local resection, radical neck dissection, and postoperative irradiation for base of tongue cancer.[67] One patient who died of distant metastasis alone was excluded from analysis of control above the clavicles. The other 13 patients had mostly moderately advanced cancers (1 stage II, 9 stage III, 2 stage IVA [both T3N3A], and 1 stage IVB [T2N3B]). After 5000 cGy in 5 weeks for patients with negative margins or 6000 to 6600 cGy for patients whose margins were close or involved, failure above the clavicles occurred in 8 (62%) of 13 patients.

University of Florida Experience

In describing the University of Florida technique of postoperative irradiation, the head and neck area is conceptually divided into three separate areas[3]:

Primary area—covers the tumor bed and adjacent tissues anterior to the plane of the mid vertebral body

Upper posterior cervical area—includes the tissues behind the plane of the mid vertebral body (this area receives less than the specified tumor dose when the primary field is reduced to limit the dose to the spinal cord, unless a boost dose is given with the electron beam)

Low neck area—covers the supraclavicular and low jugular lymph nodes and the stoma

The tumor dose was usually calculated at midline. The mean and median tumor doses in 134 patients who completed irradiation were 6300 and 6500 cGy, respectively, with a range of 4500 to 7200 cGy. Three additional patients received less than 4500 cGy because they terminated irradiation prematurely. The mean and median dose per fraction was 185 cGy with a range of 155 to 215 cGy. All patients were treated once a day, 5 days a week. The dose to the posterior cervical field on one or both sides of the neck was boosted in 60 of 134 patients (45%) with 6- to 10-MeV electrons through a lateral portal. The given dose (at Dmax) to the low neck in the majority of cases (102 patients) was 4700 to 5000 cGy in 25 fractions; 22 patients received 5700 cGy in 29 to 32 fractions.

CONTROL OF DISEASE ABOVE THE CLAVICLES. The majority (21 of 25, or 84%) of recurrences occurred in the primary field; recurrences in the posterior cervical field (2) and low neck (2) were equally uncommon (8% each). The rates of recurrence did not correlate with AJCC stage or individual T and N classification. For patients with invasive cancer at the margin, the 5-year actuarial rate of disease control above the clavicles was 53%, compared with 81% for patients with negative margins and 88% for patients whose margins were close (less than or equal to 5 mm) or contained carcinoma in situ.

Control above the clavicles was achieved in 21 of 33 patients (64%) with oral cavity lesions compared with 62 of 75 (83%) for the other sites combined ($P = .029$).

The interval between surgery and irradiation (less than or equal to 6 weeks versus 6 to 10 weeks) did not affect the control rate, even with stratification by status of the surgical margin, tumor dose, and number of indications for irradiation.

TIME–DOSE ANALYSES. One hundred two patients were eligible for the time–dose analysis of control of disease in the primary field. Thirty-two patients were excluded from the time–dose analysis for the following reasons: interstitial implant (1), primary site not irradiated (1), recurrence above the clavicles but outside the primary field (4), death from intercurrent disease or distant metastasis less than 2 years after irradiation with no evidence of recurrence in the primary field (26). For the purposes of the time–dose analysis, patients from each primary site category were divided into a high-risk group (invasive cancer at the margin and/or four or more indications for irradiation) and a non–high-risk group (margin free of invasive cancer and three or fewer indications) (Fig. 12-21). The only subgroup of patients for whom a dose–effect relation was demonstrated was the high-risk patients with primary lesions in the larynx and hypopharynx (see Fig. 12-21*B* and *D*). In this subgroup, doses of 6200 cGy in 6½ to 7 weeks to 7000 cGy in 8 to 8½ weeks resulted in control in 9 of 11 (82%) versus 1 of 4 (25%) at lower doses ($P = .077$). For non–high-risk patients with laryngeal and hypopharyngeal lesions, the rate of disease control in the primary field was excellent (48 of 52, or 92%). Doses of 6000 to 6500 cGy in 6 to 7 weeks appear adequate to produce a high rate of disease control (18 of 19, or 95%; see Fig. 12-21*A* and *C*).

The doses administered to patients with oral cavity lesions were generally higher than those given to patients with laryngeal or hypopharyngeal lesions (see Fig. 12-21*E* and *F*). Despite the higher doses, the control rates were poorer for both risk subgroups of patients with disease of the oral cavity compared with similar-risk patients with disease in the larynx or hypopharynx. For non–high-risk patients with oral cavity disease the primary field control rate was 17 of 21 (81%), compared with 48 of 52 (92%) patients with non–high-risk larynx or hypopharynx disease ($P = .160$). For oral cavity patients in the high-risk group, the primary field control rate was 4 of 9 (44%), compared with 10 of 15 (67%) for the larynx and hypopharynx ($P = .260$). Five patients with primary lesions in the oropharynx were not included in the time–dose analysis because the number was too small for meaningful conclusions.

For the analysis of recurrence in the posterior cervical field, 49 patients were excluded because they first developed recurrent disease elsewhere above the clavicles (primary field, 21 patients; low neck field, 2 patients) or died of intercurrent disease or distant metastasis less than 2 years after irradiation with no evidence of recurrence above the clavicles (26 patients). In the remaining 85 patients (170 heminecks), there were two recurrences in the posterior cervical field (1%). The recurrence rate as a function of the status of the hemineck was as follows: 2 of 114 (2%) in the clinically or pathologically negative hemineck and 0 of 56 in the pathologically positive hemineck. Both of the recurrences occurred in undissected, clinically negative heminecks that did not receive a boost dose after reduction of the field off the spinal cord after 4700 and 5000 cGy, respectively. To determine if there was a dose–response relation for control of disease in the posterior cervical field, the dose at a depth of 2 cm was calculated for each hemineck separately, taking into

account both ipsilateral and contralateral prereduction fields as well as electron boosts. When the posterior cervical field received less than or equal to 5000 cGy, the recurrence rate was 2 of 116 (2%), compared with 0 of 54 with a dose of more than 5000 cGy ($P = .464$).

For the analysis of control of disease in the low neck field, 49 patients were excluded because they first developed recurrence elsewhere above the clavicles (primary field, 21 patients; posterior cervical field, 2 patients) or died of intercurrent disease or distant metastasis less than 2 years after irradiation with no evidence of recurrence above the clavicles (26 patients). Two recurrences were noted (2 of 85, or 2%). One occurred in the soft tissues of the neck outside the radiation field; this patient was excluded from the dose analysis. The other recurrence was in the stomal area. The recurrence rate was 0 of 41 for patients who received less than or equal to 5000 cGy (at Dmax) versus 1 of 43 for doses greater than 5000 cGy. The dose to the low neck exceeded 6000 cGy in only 9 patients.

For the analysis of disease control in the stomal area, of 91 patients with lesions of the larynx or hypopharynx, 37 were excluded because they died 2 years or less after irradiation with no evidence of recurrent disease above the clavicles (21 patients), had recurrence above the clavicles other than in the stoma (9 patients), or underwent supraglottic laryngectomy (7 patients). The stomal recurrence rate in the remaining 54 patients was 1 of 54 (2%). In patients whose tumor extended 5 mm or more below the free edge of the vocal cord, the stomal recurrence rate was 1 of 18 (6%), versus 0 of 36 in patients in whom such extension was not present. The recurrence rate according to given dose (at Dmax) and disease extent was as follows: with less than 5 mm subglottic extension, less than or equal to 4600 cGy, 0 of 9; 4700 to 6000 cGy, 0 of 26; and 6100 to 7000 cGy, 0 of 1; with greater than or equal to 5 mm subglottic extension, less than or equal to 4600 cGy, 0 of 1; 4700 to 6000 cGy, 1 of 14; and 6100 to 7000 cGy, 0 of 3.

There was no significant relation between tumor dose and survival (data not shown). Further analysis of the University of Florida data is given in Chapter 5.

Treatment Guidelines

For patients with lesions of the larynx or hypopharynx who have indications to receive postoperative irradiation, our policy is to treat the primary field with 6000 cGy over 6 weeks to 6500 cGy over 7 weeks if the surgical margin is free of invasive cancer and there are three or fewer indications for irradiation. The tumor dose is increased to 6500 to 7000 cGy in 6½ to 8 weeks if there is invasive cancer at the surgical margin or if there are four or more indications for irradiation.

For lesions of the oral cavity or oropharynx, when the surgical margin is free of invasive cancer, the tumor dose is 6000 to 6500 cGy in 6 to 7 weeks if there are three or fewer indications for irradiation and 6500 to 7000 cGy in 6½ to 7½ weeks if four or more indications are present. For patients with invasive cancer at the margin, the results for oral cavity patients have been lower than for other primary sites. Alternative fractionation schemes (eg, twice-a-day fractionation) are being considered for these patients.[135] In occasional patients, the addition of an interstitial implant may be feasible.

The use of the electron beam to boost the dose to the posterior cervical area is highly individualized. For patients at high risk for disease recurrence in the neck (ie, multiple positive nodes, extracapsular extension, soft tissue extension), the total dose to the posterior cervical area (at 2 cm depth) is usually 5500 to 6500 cGy. Patients at lesser risk receive 5000 cGy to the area.

The low neck usually receives 5000 cGy given dose (at Dmax) in 25 fractions. A reduced field or electrons may be used to boost the dose to high-risk areas of the low neck (eg, stoma) to 6000 to 6500 cGy as needed.

Split-Course Irradiation in the Postoperative Setting

In a separate analysis, 27 patients who received planned split-course postoperative irradiation at the University of Florida were compared with the 134 patients who received continuous-course postoperative irradiation.[2] At 5 years, the probabilities of control above the clavicles, overall survival, and cause-specific survival were significantly higher in the continuous-course group. A stepwise multivariate analysis confirmed that the type of irradiation course (split versus continuous) was an independent prognostic variable of statistical significance for both control above the clavicles and death with cancer present. The incidences of acute intolerance (4%) and late complications (7%) were the same in the split- and continuous-course groups.

Preoperative Irradiation

Low-Dose (Less Than or Equal to 3000 cGy) Preoperative Irradiation

Low-dose preoperative irradiation may diminish the ability of cancer cells to implant in surgical wounds or distant sites.[83,129] Several trials have been conducted in head and neck cancer patients (Table 12-21).[87,92,166] In the Medical College of Virginia and Memorial Sloan-Kettering Hospital trials, local results are given with minimum 6- and 12-month follow-up, respectively; that is, patients who died of other causes before 6 or 12 months with disease controlled were excluded from analysis. There was no period of minimum follow-up in the National Cancer Institute study. All three trials showed modest reductions in the rates of local–regional recurrence but not enough difference to affect survival rates.

At M.D. Anderson Hospital, 2000 cGy in five fractions was used preoperatively for 10 stage III and IV squamous cell carcinomas of the oral cavity.[72] Five (63%) of eight evaluable patients suffered recurrence above the clavicles; the technique was quickly abandoned. The schedule was particularly inefficacious when there was perinodal tumor extension into the connective tissues of the neck.

At Washington University, medium-dose irradiation (3000 cGy over 3 weeks to the midline, usually from a single ipsilateral field) followed by resection was for many years a common treatment strategy. Marks and coworkers[105] analyzed 137 patients with carcinoma of the pyriform sinus who received preoperative irradiation followed by partial laryngopharyngectomy or total laryngectomy-partial pharyngectomy and ipsilateral neck dissection. The authors noted significant rates of failure at the primary site and ipsilateral neck (see Chap. 20). Fixed lymph nodes rarely (2 of 11, or 18%) became resectable. The clinically negative contralateral neck (which received about 2500 cGy over 3 weeks) was also a

frequent site of failure (20 of 137, or 15%). The authors concluded that the preoperative doses were too low and that operation and high-dose postoperative irradiation for advanced lesions would likely result in fewer recurrences and would produce less morbidity than high-dose preoperative irradiation.

High-Dose (4500 to 5500 cGy) Preoperative Irradiation

The literature regarding the relative roles of preoperative and postoperative irradiation and the morbidities of the two approaches is conflicting. Some authors report

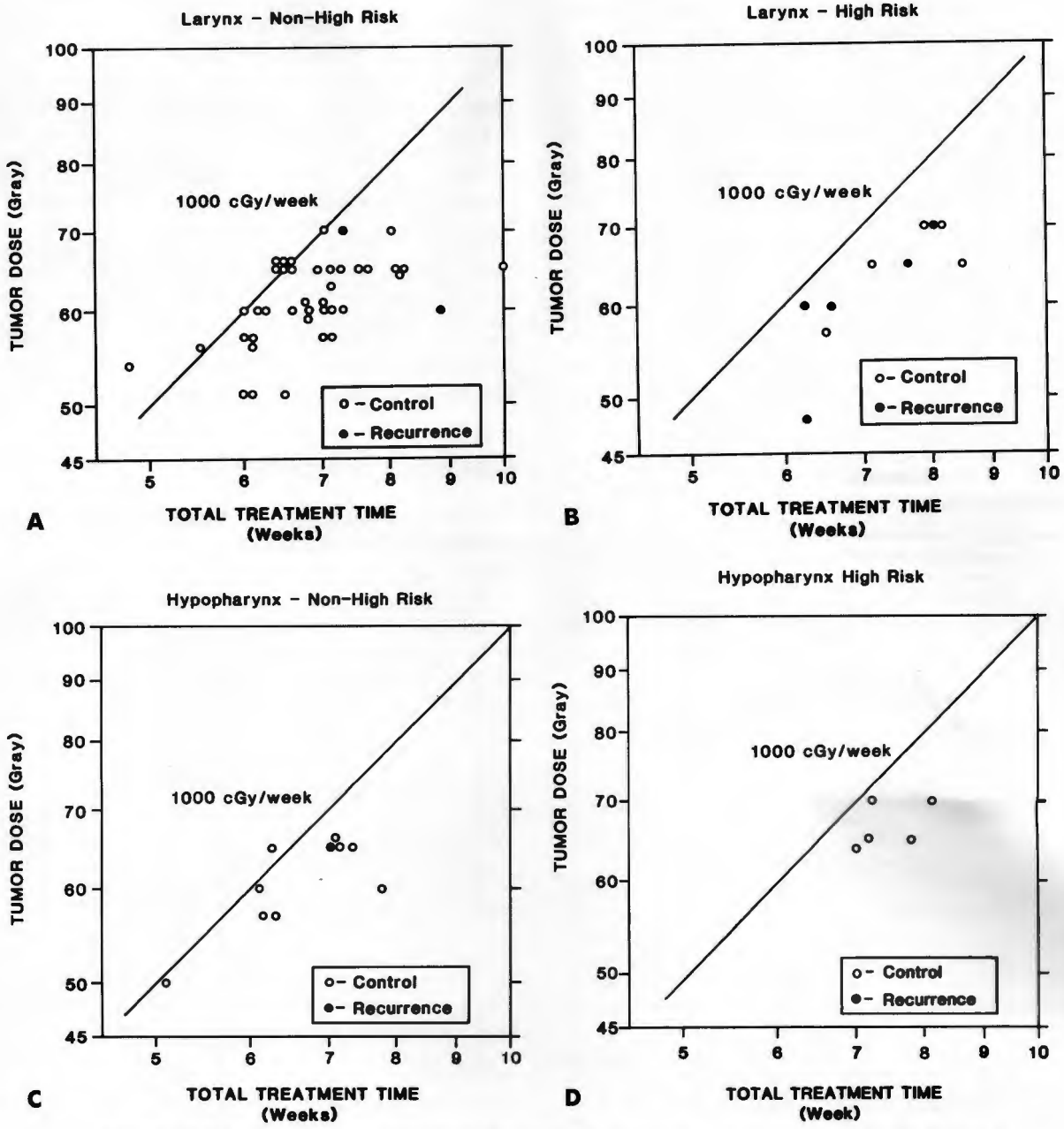

Figure 12-21. Time–dose scattergrams for control of disease in the primary field by site and risk group. High risk, four or more indications for irradiation or invasive cancer at the surgical margin; non–high risk, three or fewer indications and margin free of invasive cancer. In each scattergram, the line indicating 1000 cGy/wk is a reference line and does not represent isoeffect combinations. (*A*) Larynx, non–high risk. (*B*) Larynx, high risk. (*C*) Hypopharynx, non–high risk. Not shown is a recurrence at 3800 cGy in 4½ weeks. (*D*) Hypopharynx, high risk. (*E*) Oral cavity, non–high risk. (*F*) Oral cavity, high risk. (Amdur RJ, Parsons JT, Mendenhall WM, Million RR, Stringer SP, Cassisi NJ. Postoperative irradiation for squamous cell carcinoma of the head and neck: an analysis of treatment results and complications. Int J Radiat Oncol Biol Phys 1989;16:31)

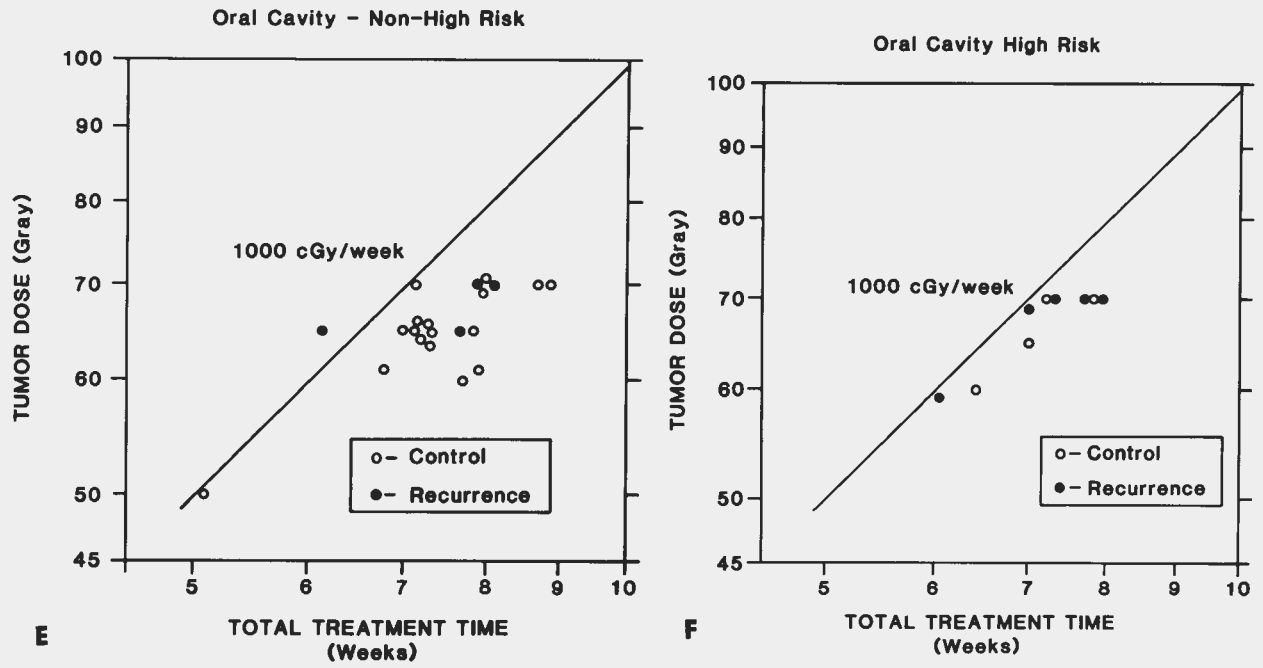

Figure 12-21 *(Continued)*

no increase in operative morbidity or mortality from doses of 5000 to 5500 cGy administered preoperatively compared with surgery alone,[68,100,182] but others report high rates of severe surgical complications after such doses.[183] Rather than present all of the various papers, from which no consistent conclusions can be drawn, only the results from two randomized trials comparing preoperative and postoperative irradiation, and literature supporting the conclusions of those trials, are presented.

RANDOMIZED TRIALS. Between 1973 and 1979, 277 patients with stage III or IV squamous cell carcinomas of the oral cavity, oropharynx, hypopharynx, or supraglottic larynx were randomized in RTOG study 73-03 to receive preoperative irradiation (5000 cGy in 5 to 5½ weeks followed by surgical resection 4 to 6 weeks later) or surgical resection followed by postoperative irradiation (6000 cGy in 6 to 6½ weeks to the area of the primary site and 5000 cGy to the remainder of the neck). The probability (Kaplan-Meier analysis) of local–regional control at 4 years was significantly greater in the postoperative group ($P = .04$). Survival was also higher in the postoperative irradiation group, but the difference did not reach statistical significance ($P = .10$). Death due

TABLE 12-21. Prospective Randomized Trials of Low-Dose (1000 to 2000 cGy) Preoperative Irradiation for Head and Neck Squamous Cell Carcinomas

	Memorial Sloan-Kettering Hospital[166]		Medical College of Virginia[92]		National Cancer Institute[87]	
Result	2000 R/5 days to Neck, Then Operation as Soon as Possible*	Neck Dissection Alone*	700 cGy × 2, 24 and 48 Hours Preoperatively†	Operation Alone†	1000 R 24 Hours Preoperatively‡	Operation Alone‡
Recurrence above clavicles	Not applicable; primary site not always irradiated		15/63 (24%)	24/63 (38%) ($P = .13$)	12/60 (20%)	6/18 (33%) ($P = .14$)
Neck recurrence with primary tumor controlled	23/131 (18%)	52/181 (29%) ($P = .032$)	Not given		Not given	
Distant metastasis	Not given		12/63 (19%)	11/63 (17%)	36%	30%
Major complications	No difference		No difference		21%	0
Survival	No difference		No difference		Not given	

* Minimum follow-up of 1 year.
† Minimum follow-up of 6 months.
‡ No minimum period of follow-up.

to uncontrolled primary disease was significantly more frequent in the preoperative group, whereas the rates of death due to regional or distant metastasis or to treatment complications did not differ between the two treatment groups. The rates of severe complications also did not differ between the two treatment groups.[90]

Between May 1967 and February 1969, a randomized trial comparing 5500 cGy preoperatively or postoperatively for pyriform sinus, aryepiglottic fold, or arytenoid carcinomas was conducted in France.[183] The operation was the same in both groups: total laryngectomy, partial pharyngectomy, and ipsilateral radical neck dissection. Results of the trial favored postoperative irradiation in terms of both survival and morbidity (Table 12-22).

MEDICAL COLLEGE OF WISCONSIN RESULTS. Byhardt and Cox noted a 60% rate of failure above the clavicles and a 5-year survival rate of only 12% in 35 patients who received high-dose (mean, 5800 cGy in 5½ weeks) preoperative irradiation and surgery for moderately advanced cancer of the pyriform sinus.[27] The rate of development of pharyngocutaneous fistula increased with dose (17% after 5000 to 5500 cGy versus 36% after 6000 to 7000 cGy) and was increased in patients who received treatment with fewer than five fractions per week.

INSTITUT GUSTAVE-ROUSSY RESULTS. In a retrospective analysis of 206 patients who received preoperative or postoperative irradiation at the Institut Gustave-Roussy for hypopharyngeal and laryngeal squamous cell carcinomas, patients were divided into three therapeutic groups: postoperative irradiation more than 4500 cGy, postoperative irradiation less than 4500 cGy, or preoperative irradiation less than 4500 cGy. Although the high-dose postoperative irradiation group had the highest proportion of advanced cases, significantly higher rates of control were observed in this group compared with the other groups.[7]

UNIVERSITY OF FLORIDA RESULTS. At the University of Florida, most patients for whom combined therapy was indicated have received postoperative irradiation. However, in certain circumstances, preoperative irradiation has been administered. Wang and coworkers[190] reported on 103 patients with squamous cell carcinomas of the oral cavity, oropharynx, larynx, or hypopharynx who received preoperative irradiation (median dose, 4725 cGy; mean dose, 4980 cGy) at the University of Florida between March 1965 and April 1985. Large or fixed lymph nodes commonly received boost doses through anterior and posterior wedged portals to 6000 to 7000 cGy after irradiation of the primary lesion was complete. Ninety-six percent of the patients had stage III or IV disease. In about one third of the patients, preoperative irradiation was administered instead of postoperative irradiation because the tumor was thought to be unresectable (eg, owing to fixed nodal disease or extensive skin infiltration). In another third of the patients, a trial of irradiation to about 5000 cGy was first given, and then, because of poor tumor regression, radiation therapy was discontinued and an operation was performed. Other reasons for preoperative irradiation included patients whose tumors had been violated (eg, by performing a tracheostomy through the tumor), delay in the availability of an operating room, and institutional policy at the time.

Although the patients who received preoperative irradiation are not entirely comparable with those who received postoperative irradiation, it is notable that the 5-year probability of control above the clavicles was substantially lower in the preoperative group (55%) than in the postoperative group (77%). Control rates according to clinical stage were as follows: stage II, 100%; stage III, 71%; stage IV, 46%. The local–regional control rate was worse in patients who received planned split-course irradiation ($P = .09$).

In an updated analysis, factors found to significantly affect control above the clavicles were the presence or absence of tumor in the resected specimen ($P = .004$), the presence of tumor at the surgical margin ($P = .026$), the presence of perineural invasion in the resected specimen ($P = .001$), and the site of the primary tumor (oral cavity and oropharynx worse than hypopharynx and larynx, $P = .025$) (Sombeck MD, unpublished study, January 1989). Factors that did not reach significance levels included the time interval between irradiation and surgery and the AJCC stage.

Treatment Guidelines

Although the bulk of available literature suggests that the results of postoperative irradiation (to 6000 cGy or more) are superior to the results of preoperative irradiation (to 5000 cGy), preoperative irradiation is unlikely to lose its place in cancer management since it continues to be necessary in (1) patients with primary lesions that require a combined approach but who have fixed lymph nodes that must first be made resectable, (2) patients whose tumors extend beyond the usual surgical confines (eg, into the dermal lymphatics or patients whose tumors have been "spilled" by performing tracheostomy through subglottic tumor or by excisional or incisional biopsy of lymph nodes), (3) patients who are to undergo gastric pull-up, (4) patients whose reconstruction and

TABLE 12-22. Randomized Trial of Preoperative Versus Postoperative Irradiation for Carcinoma of the Pyriform Sinus, Arytenoid, or Aryepiglottic Fold

Treatment	Patients Randomized	Patients Who Completed Intended Therapy	5-Year Survival	Carotid Artery Ruptures	Treatment-Related Deaths
Preoperative irradiation (5500 cGy over 5½-wk—2-wk delay—operation)	25	16	28%	6 (38%)	5 (31%)
Postoperative irradiation (operation—<4-wk delay—5500 cGy over 6 wk)	24	23	56%	0 (0%)	0 (0%)

Note: Gustave-Roussy Institute and Henri Becquerel Center data.[183]

rehabilitation might excessively delay the start of postoperative irradiation, and (5) patients who are undergoing radical courses of irradiation but whose tumors have shown little or no sign of regression after 5000 cGy.

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13

THE EFFECT OF RADIATION ON NORMAL TISSUES OF THE HEAD AND NECK

JAMES T. PARSONS

Acute Versus Late Injury

The effects of irradiation on normal tissues usually are divided into (1) acute effects, which are present both during a course of irradiation and in the immediate postirradiation period, and (2) late effects, which become manifest months to years after treatment. Although patients are concerned mostly about acute side effects, clinicians mainly fear late sequelae, since the latter may be chronic and progressive, as opposed to acute effects, which are self-limited. Most acute effects (eg, mucositis and loss of taste) are temporary; others, such as xerostomia, which develops early during a course of irradiation, are permanent if a substantial dose has been administered. Late injuries may not heal (eg, radiation myelitis), or may heal spontaneously, as in many instances of soft tissue and bone necrosis.

Acute and late effects often are dissociated; that is, the severity of one generally does not predict the severity of the other. A patient with moderate or severe acute side effects may not have late injury, whereas another with minimal acute reaction may develop severe late complications. Dissociation between the two types of injury is most commonly seen in hypofractionated regimens that employ a small number of large-dose fractions where the weekly dose rate is often low (eg, one or two fractions a week), leading to mild acute reactions but possibly severe late effects (depending on the total dose). Likewise, although split-course programs ameliorate acute effects, they do not reduce the incidence of late effects. When acute reactions are extremely severe, late effects evolve as a direct consequence of acute injury; these are called *consequential late injuries*.[164] Consequential late injury develops when complete epithelial denudation occurs with no surviving cells within the irradiated volume such that healing, if it occurs at all, must take place entirely by repopulation of cells from the periphery of the irradiation field (see Chap. 12).

More is known about the mechanism of acute injury than of late injury. In general, tissues with rapidly dividing cell populations (eg, mucous membrane and skin epithelium) respond acutely, and those with slowly proliferating or nonproliferating cells (eg, connective tissue and spinal cord) are affected later.

Although an obvious precipitating cause of late complications sometimes exists, such as trauma or thermal injury, the exact mechanism of most late injuries is incompletely understood. Two major schools of thought exist: one theory states that irradiation injury of the microvasculature is responsible; the other holds that late damage results from parenchymal or stromal cell death. According to the second theory, late damage differs from acute damage only in that the cells of late-responding tissues or organs do not divide rapidly, and therefore, cell death is not expressed quickly. This theory considers the microvasculature itself to be a late-responding tissue that, when injured, further contributes to late injury. Fibroblast dysfunction also may be important.[104]

Late complications are, in part, dependent on the total dose and volume of tissue irradiated. Because large tumors require both higher total doses and larger treatment volumes than small lesions, a certain complication rate may be expected when controlling advanced cancer by irradiation alone. At times, it is preferable to treat advanced cancer by a combination of surgery and irradiation, to minimize the complications that result from radical therapy using either modality alone. As discussed elsewhere (see Chap. 12), daily fraction size and the time interval between fractions are other important factors in the production of late injury. Also important is homogeneity of dose. A simple but useful way of thinking about tumor control and treatment complications is to remember that the probability of tumor control is largely de-

pendent on the minimum dose that any portion of the cancer receives, and that complications are usually dependent on the maximum dose. Generally, the dose within the tumor volume should be as homogeneous as possible* to minimize the risk of localized underdosage or overdosage. Large inhomogeneities of dose within the treatment volume result not only in areas of overdosage, but the overdosed tissues also receive treatment at an increased dose per fraction, thereby increasing not only the total physical dose but also the biologic dose.

* While homogeneity is an important goal in treatment planning, it is not essential to cure a cancer. Orthovoltage irradiation through a "sieve" (a perforated lead sheet used to increase skin tolerance)[206] produced an irregular dose distribution, yet cured some head and neck cancers. Likewise, the dose within an interstitial implant may be inhomogeneous, yet may still effect a cure.

Treatment of All Portals at Each Therapy Session

When treating cancer of the head and neck by irradiation, two or more treatment portals usually are employed. Although treating only one field at each therapy session is expedient, ideally all fields should be treated daily. In a multiportal set-up, the technique of treating only one portal daily results in an increased biologic effect on the normal tissues, as discussed by Wilson and Hall.[215]

This concept is illustrated in Figure 13-1. The plan is to deliver 6000 cGy in 30 fractions to the midplane with cobalt-60 (^{60}Co) using a two-field technique. The patient's thickness is 16 cm, and field sizes are 10 by 10 cm. In plan A, only one field is treated each day. The daily midplane dose is 200 cGy; point P, lateral to the mid-

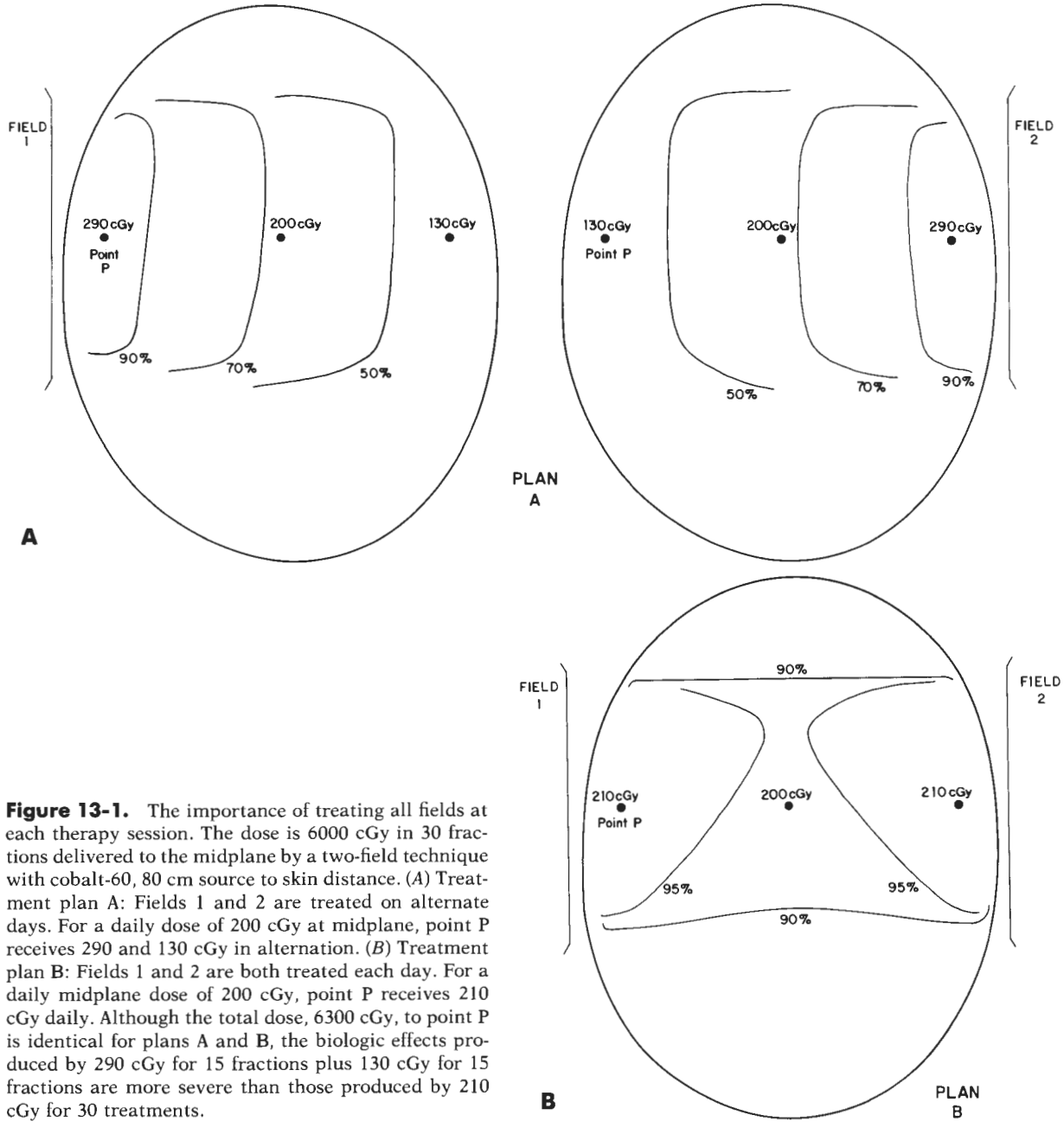


Figure 13-1. The importance of treating all fields at each therapy session. The dose is 6000 cGy in 30 fractions delivered to the midplane by a two-field technique with cobalt-60, 80 cm source to skin distance. (*A*) Treatment plan A: Fields 1 and 2 are treated on alternate days. For a daily dose of 200 cGy at midplane, point P receives 290 and 130 cGy in alternation. (*B*) Treatment plan B: Fields 1 and 2 are both treated each day. For a daily midplane dose of 200 cGy, point P receives 210 cGy daily. Although the total dose, 6300 cGy, to point P is identical for plans A and B, the biologic effects produced by 290 cGy for 15 fractions plus 130 cGy for 15 fractions are more severe than those produced by 210 cGy for 30 treatments.

plane, receives 290 cGy and 130 cGy on alternating days. In plan B, both fields are treated daily. The daily midplane dose, 200 cGy, is the same as that in plan A; point P receives 210 cGy on each of the 30 treatment days.

The total absorbed dose at point P, 6300 cGy, is identical for the two plans (290 cGy for 15 treatments plus 130 cGy for 15 treatments in plan A, versus 210 cGy for 30 treatments in plan B). Wilson and Hall showed that the biologic consequences at point P of the one-field-per-day technique (plan A) are more severe than the effects of the two-fields-per-day technique (plan B) because of the deleterious effects of large-dose fractions received by point P in plan A.[215] In Figure 13-1, if point P happens to represent an important structure (eg, the spinal cord, mandible, or pterygoid musculature), then plan A is more likely to cause a late treatment complication. This difference also has been observed among patients who received pelvic irradiation by a four-field box technique; skin and subcutaneous changes were more severe when only one field was treated each day than when four fields were treated daily. Although this observation was first made in 1950, it was years before its significance was widely recognized.[146]

For small field separations, such as in the treatment of early vocal cord cancer, little biologic difference exists between treating one versus two fields per day, and the one-field-per-day scheme is acceptable.

ACUTE EFFECTS

Mucous Membranes

Oral Cavity, Pharynx, and Larynx

The mucous membranes of the upper aerodigestive tract respond early during a course of fractionated external-beam irradiation. With five 200-cGy fractions per week, mucosal erythema develops within 1 week. At about 2 weeks, the reddened mucous membrane develops small white or slightly yellow patches, 2 to 3 mm in diameter, called *mucositis*, or *false membrane formation*. Mucositis represents caking of dead surface epithelial cells, fibrin, and polymorphonuclear leukocytes on a moist background. Patients usually note a sore throat at 2 weeks. In many patients, the patches of mucositis become confluent by the third week.

Mucositis is sensitive to changes in daily dose of radiation. At 170 to 180 cGy five times weekly, the maximal reaction usually is only intense erythema, with an occasional patch of mucositis, even when large volumes are irradiated (eg, for cancer of the nasopharynx or advanced cancer of the oral cavity); in this situation, the cell-killing and repopulation of mucous membrane stem cells are essentially in equilibrium. If the daily dose is more than 200 cGy and the treatment volume is large, cell killing exceeds the proliferative capacity of the mucous membrane stem cells; almost all patients develop confluent mucositis by the third week, which produces severe discomfort and often limits adequate nutrition. At the University of Florida, doses of 225 cGy per fraction are used only for very limited fields (eg, early vocal cord cancer).

The soft palate, tonsillar pillars, buccal mucosa, lateral border of the tongue, pharyngeal walls, and portions of the larynx readily develop mucositis. Other sites, such as the hard palate, gingival ridges, dorsum of the tongue, and true vocal cords, either develop no mucositis during treatment or develop it only after very high doses.[41] Coutard noted that mucositis often first appears over the tumor itself, sometimes as early as 5 to 7 days into treatment (ie, a week before the appearance of mucositis over the normal mucous membranes).[42] This early reaction is frequently dubbed *tumoritis*, and is most often observed when treating carcinomas of the soft palate and anterior tonsillar pillar.

Sore throat is usually greatest 2½ to 3 weeks into therapy; thereafter, the pain often diminishes, even though therapy is continued. While patients are under treatment, the mucous membranes should be examined at least weekly, since the distribution of the mucosal reaction confirms adequate tumor coverage and acts as a biological dosimeter.

Patients with gold-crown dental restorations develop pronounced mucositis on the adjacent buccal mucosa and tongue, secondary to backscattered low-energy electrons. Since the range of these electrons is short, excessive mucositis can be prevented by placing a few millimeters of moistened gauze or paraffin between the mucosa and the teeth. During a course of radiation therapy that encompasses the oral cavity, the topical broad-spectrum antimicrobial chlorhexidine (15 mL, swish and gargle for 30 seconds, then expectorate, three to four times each day) is routinely prescribed and reduces the severity of oral mucositis.[65] The substance is bound to the mucosal surfaces and is slowly released. It is effective against anaerobic and aerobic bacteria as well as against *Candida*. Chlorhexidine has little role in preventing mucositis in the larynx or hypopharynx, since it must remain in contact with the mucosal surfaces to be effective. Therapy is continued after irradiation until the soreness subsides.

After external therapy, the mucous membranes normally heal dramatically at 2½ to 3 weeks, although occasionally patients require a longer time to heal. Until that time, little change is obvious, either objectively or subjectively; the sore throat then suddenly subsides and improves rapidly over the next 2 to 3 days. After a month, the mucosa is healed in 90% to 95% of patients, and sore throat is absent or minimal.

The mucositis produced by a 7-day radium implant appears 7 to 10 days after removal, and is maximal about 2 weeks after removal. The reaction usually subsides by 6 weeks, unless the implanted volume was large, in which case complete healing sometimes requires several months.[127]

Nasal Cavity

High-dose irradiation of the anterior nares produces a brisk mucosal reaction. The moist mucosal surfaces tend to adhere to each other during the healing phase; unless measures are taken to prevent formation of synechiae, complete or nearly complete stenosis of the anterior nares may occur within 1 or 2 months after treatment. Because of their rigid, bony framework, the surfaces of the posterior nares are not in apposition, and posterior stenosis does not occur. During the first month after treatment, patients are advised to pass a long, cotton-tipped applicator stick covered with petrolatum along the length of the nasal cavity and to douche the nasal cavity with a dilute saline solution (Fig. 13-2). Both procedures should be performed twice daily until healing is complete, after which the petrolatum may be discontinued if patients desire. Regular douching is recommended indefinitely, since this helps clear the crusts and debris

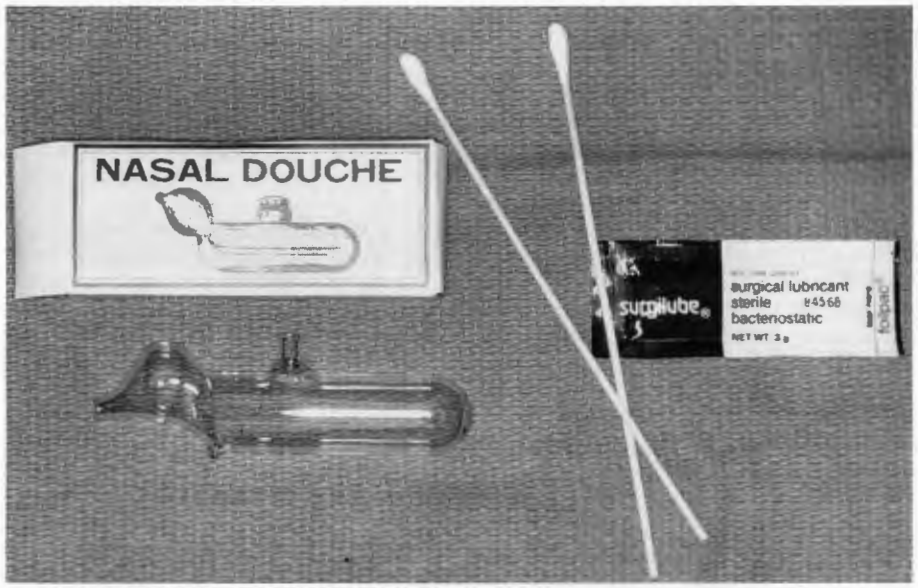


Figure 13-2. Nasal douche device and long cotton-tipped applicators used by patients after high-dose irradiation to the nose.

that tend to collect on the dry membranes. If at the time of the first follow-up examination patients are already developing stenosis, the synechiae usually can be lysed with the use of topical anesthesia; patients then are asked to use the applicators more frequently and to return to the clinic on a weekly basis until the problem is resolved. If complete stenosis develops, surgical division is necessary.

Conjunctiva

During a course of ^{60}Co irradiation for cancer of the paranasal sinuses, patients typically develop mild or moderate symptoms of conjunctivitis (foreign-body sensation and occasionally photophobia) and lid irritation. Unless all of the lacrimal tissue has received a high dose, these symptoms generally resolve within 4 to 6 weeks after treatment.

Sense of Taste

Taste buds are numerous on the circumvallate papillae. They are found in moderate numbers on the fungiform papillae, which are scattered all over the anterior two thirds of the tongue, and on the foliate papillae along the posterolateral surfaces of the tongue. Additional taste buds are located on the tonsillar pillars, base of the tongue, soft palate, and laryngeal surface of the epiglottis, and a few are found on the posterior pharyngeal wall. The filiform papillae of the tongue possess no taste buds. Taste buds atrophy with age; those on the posterior third of the tongue and on the epiglottis usually disappear early in life.[212] The taste buds that mediate each of the four primary taste sensations tend to be localized in special areas of the tongue: sweet on the anterior surface and tip, sour on the lateral sides, bitter on the circumvallate papillae, and salty all over the tongue.[82]

Taste loss begins about 1 week into the course of irradiation and then progresses rapidly between 2000 and 4000 cGy. Salivary dysfunction precedes taste loss and, unlike taste loss, occurs without any apparent threshold.[143] Some patients report a bitter taste during the early part of treatment, but most simply state that taste is diminished. The higher the pretreatment taste acuity, the more rapid is the loss.[37] Acuity is essentially absent by the end of the third treatment week, although a few patients report minimal changes even by the end of therapy. The mechanism by which taste is impaired is unknown. Conger suggests that taste loss is due to damage to the microvilli of the taste cells, and he has performed electron-microscopic studies in mice that show loss of microvilli after irradiation.[37] After therapy is finished, acuity of taste recovers rapidly at first, then more slowly; most patients report some improvement within 20 to 60 days.

Salivary Tissue

The normal human salivary glands produce 1000 to 1500 mL of saliva each day, most of which is recycled by the gut.[55] The major salivary glands account for 70% to 80% of the salivary flow; the remaining flow comes from minor salivary glands that are scattered throughout the mouth. Under resting conditions, the flow from the submandibular glands is at least as great as that from the parotid glands, or possibly greater[62,186]; the sublingual glands contribute only 2% to 5%.[138] Under conditions of stimulation (eg, eating or drinking), the parotid glands become the main contributors. In humans, the parotid glands consist entirely of serous acini. The submandibular glands contain both mucous and serous acini[172]; the minor salivary glands are predominantly mucus secretors.

In addition to decreased flow, irradiation produces an increase in salivary sodium concentration, a decrease in pH level, and an increase in oral yeast flora.[55,106] Clinical symptoms correlate with the amount of salivary tissue irradiated.

Xerostomia

If only the submandibular and sublingual glands are included in the treatment area, and not both parotid glands, most patients note little subjective difference in their saliva; even in this setting, however, the salivary flow is altered so that dental caries becomes a problem and fluoride prophylaxis is necessary. If one or both parotid glands are irradiated, along with the submandibular glands, the sensation of dryness is noted after only a few treatments. During a course of ^{60}Co irradiation, Mossman noted 50% loss of flow in patients after only 1000 cGy, followed by continual, but less rapid, loss as treatment progressed.[143] If the parotid glands are irradiated and the submandibular glands spared, moisture may be preserved.[138,186]

A few patients report little subjective change, even after radical courses of irradiation, but most note partial to complete loss of salivary function. If both parotid glands, both submandibular glands, and a large number of minor salivary glands are included in the treatment area (eg, as in cancer of the nasopharynx), severe dryness results. Presumably because the serous acini are affected earlier than the mucous acini, the saliva first becomes thick, sticky, and ropy. Patients often have considerable difficulty handling these tenacious secretions in their dry mouths. Continued use of tobacco and alcohol produces an additional drying effect. Patients are instructed to rinse and gargle with a solution of salt and soda several times daily, both during the course of irradiation and until mucosal healing is complete. The solution consists of a teaspoon each of table salt and baking soda in a quart of water, and it serves to refresh the mouth, decrease the pain from mucositis, and loosen the thick, tenacious saliva. Commercial preparations of artificial saliva are available, but few patients use them, often stating that the solutions have an unpleasant taste.

Sialadenitis

Within 12 hours of the first treatment, about 5% of patients develop a transient, usually painless, enlargement of one or more of the salivary glands within the treatment portal. Occasionally, mild pain and tenderness occur, but usually symptoms are limited to a "tight" sensation. In contrast to acute suppurative parotitis, systemic symptoms are minimal or nonexistent. Patients often are alarmed and call the physician just after eating, thinking that the cancer is growing rapidly in the neck. The swelling has been noted more frequently in the submandibular glands than in the parotid glands, but either may occur, and one or both sides may be affected. The swelling usually disappears within 1 or 2 days despite continuation of treatment. Simultaneous with the swelling and its resolution is a rise and fall in the serum amylase level.[98] The physician should anticipate the problem and warn patients in advance.

Skin and Subcutaneous Tissues

The skin consists of two layers, epidermis and dermis, beneath which is a subcutaneous layer containing varying amounts of adipose tissue. The epidermis is a stratified squamous epithelium, entirely devoid of blood vessels; its deepest cells constitute the basal layer, which, in the head and neck area, is at an average depth of 0.03 to 0.05 mm.[214] Mitotic activity in the basal layer forms new cells to replace the superficial keratinized cells that are continually exfoliated from the skin surface. Melanin granules are formed by melanocytes in the deep layers of the epidermis and are transferred into neighboring epidermal cells. Tubular invaginations of the epidermis (called hair follicles) surround each hair shaft and extend deep into the dermis.

The dermis consists mostly of dense connective tissue and contains nerve endings, blood and lymph vessels, and sweat and sebaceous glands. The ducts of sweat glands discharge onto the epidermal surface, and those of sebaceous glands discharge into hair follicles. It is difficult to measure precisely the thickness of the dermis, since its boundary with the subcutaneous layer is indistinct; it is 1 to 2 mm thick in the head and neck area.[193]

In the orthovoltage era, treatment plans were dictated by the limits of skin tolerance. Rarely, in the modern era of supervoltage therapy, is the skin a major dose-limiting tissue per se. High-energy x-rays are *skin-sparing*; that is, the buildup characteristics of the absorbed dose are such that the skin receives a low dose relative to deeper structures. Skin-sparing is lost or reduced when tissue-equivalent material, called bolus, is placed on the skin; when the beam enters the body tangentially, rather than perpendicular to the skin surface; or when the lead blocks and blocking tray used to shape the x-ray fields are too close to the patient (see Chap. 14). When tumor actually invades the skin and subcutaneous tissues, or when tumor cells have been seeded in surgical scars, skin-sparing is undesirable and steps are taken to ensure an adequate skin dose.

When parallel–opposed ^{60}Co fields are treated to tumor doses in the range of 7000 to 7500 cGy (five 180- to 200-cGy fractions per week), acute skin effects are limited to erythema, peeling, and tanning. These changes are reversible. Erythema often is noted first around hair follicles, since the invaginations of epidermis receive a higher dose than cells on the skin surface; follicular erythema more often is seen in the lower neck fields than in the primary fields. Peeling (or dry desquamation) of the skin results from radiation killing of basal cells in the epidermis. Scales of skin (which are sometimes dark because radiation stimulates melanin production) result from caking of dead cells, a situation analogous to that seen on the mucous membranes (mucositis). As with a sunburn, patients note increased sensitivity to touch and complain of itching and drawing until healing is complete, 2 to 3 weeks after completion of therapy.

If the skin has been irradiated tangentially or with bolus, then the capacity of the basal cell layer to repopulate the epidermis may be exceeded and patients may develop areas of complete epidermal denudation, called *moist desquamation,* a medical euphemism for a radiation burn. The dermis is exposed and oozes serum. Although the appearance alarms physicians unfamiliar with the reaction, healing generally occurs spontaneously within 2 to 4 weeks, depending on the area involved and unless infection supervenes. Areas of moist desquamation should be kept clean; remove crusts by soaking with a dilute hydrogen peroxide solution. Gentian violet (1% aqueous solution) can be applied for its bactericidal and fungicidal properties as well as for the eschar that it forms. Reepithelialization occurs from the periphery of the field and, if the dose has not been too great, from single surviving cells in the middle of the field.

Epilation of the beard usually begins during the third week of treatment. Sweat and sebaceous glands cease to function.

Acute skin reactions vary with the size of the area irradiated, dose, overall treatment time, number of fractions, quality of radiation, and other patient-related variables, including degree of pigmentation, age, and site irradiated.

For the same dose, the face reacts less vigorously than the upper neck, and the upper neck reacts less than the lower neck and supraclavicular area. The skin response thus is related to relative exposure to sun.

LATE EFFECTS

Salivary Tissue

Xerostomia

Xerostomia causes discomfort, alters taste acuity, contributes to deterioration of oral hygiene, and promotes dental decay. The remaining saliva has an altered electrolyte content and reduced pH level. Histologically, the heavily irradiated gland is obliterated and largely replaced by collagen.

Loss of salivary function is usually complete and permanent after doses larger than approximately 3500 cGy. In patients with extremely low flow rates before irradiation, lesser doses cause permanent dryness. Marks and coworkers found that only one fifth of patients whose parotid glands had received 4000 to 6000 cGy had any measurable parotid flow after salivary stimulation; above 6000 cGy, none of 24 parotid glands had measurable flow.[125] Although occasional patients report improvement in the sensation of dryness several years after treatment, objective recovery of salivary flow has not been documented in such cases. If the salivary tissue received less than 3000 to 3500 cGy, often some function returns during the 6 months after therapy. Makkonen and colleagues noted partial recovery of salivary flow in the 12 months after therapy in most patients whose glands received 3100 to 4600 cGy, whereas patients whose glands received 5800 to 7000 cGy had permanent xerostomia.[120] The authors noted, however, that the upper part of the parotid gland was usually outside the radiation portals in the low-dose group, thereby improving the chances for recovery. Young patients are more likely than older patients to recover salivary flow. During treatment planning, one should limit the volume of salivary tissue irradiated and the dose delivered when possible. Minor changes in field size and shape may preserve some salivary flow. If more than half of the parotid tissue receives a high dose along with the rest of the major salivary glands, significant xerostomia usually results. Patients with high pretreatment salivary flow develop less dryness after a particular dose[138] or treatment volume[31] than those with low pretreatment flow rates.

The decrease in flow after irradiation follows an exponential decay curve. A certain dose reduces flow by about the same percentage, not by the same absolute amount, in two patients. A patient whose initial salivary flow rate is 0.2 mL/min would require a reduction of only 50% to reach a minimal flow rate (0.1 mL/min), whereas a patient whose flow rate is 1 mL/min would require a 90% reduction to reach the same level of flow. The latter patient would require about three times more irradiation as the former to reach 0.1 mL/min. Based on resting collections from all of the salivary glands, Mira and coworkers showed that during courses of irradiation that included almost all of the salivary tissue, 3500 to 4000 cGy was capable of inducing minimal flow (0.1 mL/min or less) in patients with high initial flow rates (0.9 to 1.5 mL/min); 50 to 1500 cGy resulted in minimal flow in patients with low (0.15 to 0.4 mL/min) initial flow rates.[138] Patients in whom minimal flow rate was induced during irradiation showed no recovery of flow in samples taken 1 to 17 months after treatment. Although Mira and coworkers have suggested that split-course irradiation might protect salivary tissue, this effect has not been observed at the University of Florida.[159]

Patients with significant xerostomia get some symptomatic relief by using one of the commercially available artificial saliva preparations. These solutions have a pH of about 7.0 and a consistency similar to saliva. Some patients carry a bottle of artificial saliva with them at all times, others use plain or flavored glycerin to lubricate their mouths, but most use water.

Sialadenitis

Submandibular or parotid gland infection is sometimes seen after high-dose irradiation. Sometimes fever is present, and patients may have marked pain and tenderness; in other patients, the pain is intermittent. At the University of Florida, 6 of 419 patients who received high-dose, twice-a-day irradiation for cancer of the oral cavity, oropharynx, larynx, or hypopharynx developed sialadenitis at 1½, 2, 3, 4, 5, and 7 months postirradiation, respectively. Purulent debris could be easily expressed from Wharton's or Stensen's ducts in all patients; this debris was sent for culture. This complication probably is due to relative obstruction to flow in the heavily irradiated gland, inspissation of salivary secretions, and some degree of dehydration. Minimally symptomatic patients can be treated as outpatients with oral antibiotics, hydration, and sialagogues. Febrile or markedly symptomatic patients are treated with intravenous antibiotics. All six patients from the University of Florida responded to treatment, with resolution of symptoms over a period of several days to weeks.

Sense of Taste

Subjective recovery of preirradiation taste acuity is usually complete by 60 to 120 days after treatment.[37] Some patients state that their taste is never as sharp as before treatment, but it is usually adequate. Mossman and coworkers noted that many patients who have no subjective complaints of taste loss have measurable losses (most commonly for salt and bitter) when sophisticated testing is performed.[145] On rare occasions, patients report little or no improvement for many months or years after treatment. At least part of this subjective loss is due to xerostomia, which itself affects taste acuity. Mossman and Henkin, as well as Silverman and Thompson, suggest that zinc therapy is useful in alleviating symptoms in some patients whose sense of taste does not completely return to normal after therapy; the trials were not controlled, and the tentative results require verification by other investigators.[144,191]

Teeth

The pathologic changes that occur in the teeth secondary to irradiation are mainly due to diminished salivary flow, rather than being a direct effect on teeth or surrounding bone. The teeth are affected regardless of whether they are inside or outside of the radiation field. If the salivary glands are not irradiated, caries does not occur as a result of treatment, even if the teeth and jaw receive high-dose radiation.

During and immediately after treatment, patients have a sore throat and a dry, sticky mouth; they stop eating a rough diet and change to a soft, high-carbohydrate diet that has little detergent value and favors the growth of plaque. Patients have a tendency to stop routine dental care because the tissues are tender. In association with radiation-induced xerostomia, the normal oral microflora shifts markedly to a highly cariogenic microbial population.[24] Unless stringent measures are taken to protect the teeth, rampant dental caries begin to develop as early as 3 to 6 months after treatment and progress to complete destruction of all the teeth over a period of 3 to 5 years.

The histologic character of radiation caries is similar to that of dental caries; the two lesions differ, however, in several important aspects. The lesions that develop after irradiation are more widespread; frequently a generalized attack on enamel occurs, beginning as fine, punctate defects that progress to larger lesions. Patients complain of hot–cold hypersensitivity and sensitivity to sweet foods.[70] Typical dental caries occurs mainly on the proximal surfaces and fissures, sites not easily reached by saliva, and therefore, prone to food retention. The lesions induced by radiation, by contrast, occur mostly on the buccal, palatal, or lingual surfaces and on the incisal and occlusal edges of the teeth. Under normal circumstances, all of these surfaces are readily bathed by saliva[70] and are usually resistant to caries. The edges of the teeth may appear as though they have been finely sanded or filed; the concentric layers around the pulp sometimes are seen in cross section.[48]

As the late effects of radiation progress over several months, shrinkage of the periodontal tissues occurs, leading to exposure of cementum. Decay occurs at the exposed cervical portion of the tooth, usually beginning on the labial or buccal surfaces, then extending superficially around the neck of the tooth to produce an annular lesion that eventually results in complete amputation of the crown. The root remains in the alveolar cavity and is slowly eliminated.[48] Before irradiation, the dentulous patient must be evaluated by a dentist (see Chap. 10).

Masticatory Muscles and Temporomandibular Joint

High-dose irradiation to voluntary muscles may produce fibrosis, particularly when cancer has invaded and partially destroyed the muscles. Fibrosis of the muscles of mastication (temporalis, masseter, and pterygoid muscles) may cause trismus. Many patients with advanced cancer of the head and neck have trismus at the time of diagnosis, secondary to local tumor extension into the pterygoid musculature. Although this symptom often disappears during the course of irradiation, it may gradually reappear in the postirradiation period if significant pterygoid muscle fibrosis develops. The temporomandibular joint itself is reasonably resistant to the ankylosis secondary to irradiation; the risk of injury increases if the joint has been invaded by tumor. Patients may complain of clicking, crackling noises and pain associated with motion at the temporomandibular joint; on examination, the exact site of injury (joint or masticatory muscles) may not be obvious.

Radiation-induced trismus occurs most often after irradiation of cancer of the nasopharynx, tonsil, retromolar trigone, or paranasal sinuses. The use of large daily fractions increases the risk of impairment of motion at the temporomandibular joint.[139] When treating cancer of the nasopharynx, the four-field technique reduces the dose to the masticatory muscles and temporomandibular joint, but unfortunately is not appropriate for most nasopharyngeal cancers (due to lateral or inferior tumor extensions into the oropharynx or low retropharyngeal lymph nodes). Since no simple treatment of severe trismus exists, avoiding the problem is paramount. If severe trismus develops, dental extractions might be necessary to permit eating.

Patients who have received both surgery and irradiation are at greater risk of developing trismus than patients treated by either modality alone. High-risk patients, and especially those in whom trismus is already beginning to develop, should perform exercises several times daily to increase the interarch distance; exercises should begin as soon as practical in the postoperative period and should continue both during and after irradiation. One technique is to have the patient insert a number of stacked tongue blades between the teeth, then successively wedge additional blades into the stack until slight pain is encountered. Alternatively, a tapered cork can be inserted between the teeth to a point where minimal discomfort is reached; over a period of days to weeks, the patient attempts to place the cork farther and farther into the mouth. Another technique uses a clothespin onto which a rubber band is tightly wound to open the mouth forcibly (Fig. 13-3). The exercises usually are done for about 30 seconds every 2 hours. The distance between the upper and lower incisors should be measured and patients should increase this distance by using the exercises to break down existing fibrosis. Most patients can function well with an interincisor distance of 35 mm for dentulous patients, or an interalveolar distance of 50 mm for edentulous patients. Early evaluation by a dentist is helpful in preventing or solving these problems.

Soft Tissue and Bone Necrosis

Radiation necrosis is a destruction of normal tissue. Necrosis is believed to be due to the avascular effect of radiation. After healing of the acute reaction of the mucous membrane, the epithelium is thinner than normal. The clinical appearance is that of a pale, hypotrophic epithelium through which telangiectatic vessels may be seen. Such mucosa is more susceptible than normal to mechanical injury and to the noxious effects of alcohol and tobacco. Necrosis usually begins with breakdown of this damaged mucosa, leaving a small ulcer.

If ulceration occurs on soft tissues that have no underlying bone, the result is a *soft tissue necrosis.* If it occurs on soft tissues of the gingiva, and no obvious sequestration or bone necrosis exists, the ulcer is called *bone exposure;* if serious injury to the underlying bone occurred,

Figure 13-3. Trismus secondary to extensive squamous cell carcinoma of paranasal sinuses, with invasion of pterygoid musculature. During the course of irradiation, the patient used a clothespin, onto which a rubber band had been tightly wound, to exercise and gradually increase the interincisor distance. Conscientious efforts should be made to reverse existing trismus or prevent its occurrence after irradiation, since it is difficult to manage once established.

bone necrosis, or *osteoradionecrosis*, is said to be present. Although the terms *bone exposure* and *osteoradionecrosis* frequently are used indiscriminately, few exposures progress to severe bone necroses.

Bone Exposure and Osteoradionecrosis of the Mandible and Maxilla

If the area of exposure is less than 1 cm, actual necrosis of the underlying bone and sequestration may not occur or may be minimal; roentgenograms appear normal. Small exposures heal spontaneously after a period of weeks to months. On the other hand, if the bone exposure enlarges and persists for a long period, bone necrosis followed by sequestration may occur. A segment of mandible or, rarely, maxilla is exposed, with apparently dead bone. Histologically, true osteoradionecrosis is characterized by damage to the cellular elements of bone, as well as vascular changes. The marrow space is infiltrated by inflammatory cells and loose connective tissue.[147] Roentgenograms show an irregular lytic defect that frequently extends beyond the clinically apparent area of destruction. Severe necrosis may lead to orofacial fistulas and pathologic fractures.

To better define the pathogenesis of osteoradionecrosis, Marx performed cultures and stains for microorganisms in the en bloc resection specimens of 12 osteoradionecrotic mandibles.[129] In contrast to specimens obtained from infected jawbone grafts or patients with osteomyelitis (in which both the bony surface and medullary portions of the bone contained microorganisms), bones that were affected by osteoradionecrosis contained microorganisms only as surface contaminants (ie, no infectious process was demonstrated deep in the bone). Marx concluded that hypocellularity and hypovascularity, not infection, were the initiating agents after irradiation.

Although a direct effect of radiation on bone itself exists, most bone, including the mandible, tolerates high doses of radiation without serious problems, so long as the tissues overlying the bone remain intact and the bone is not subjected to excessive stress or trauma. Although occasional patients develop mandibular necroses beneath normal-appearing mucous membranes, 95% of necroses are associated with soft tissue necrosis and bone exposure. Compared with the maxilla, the gingiva of the mandible has a tenuous blood supply. The mucosal covering is thin and constantly traumatized (by eating or by wearing dentures, for example). Once mandibular necrosis occurs, it is difficult to obtain healing. Necroses of the maxilla occur less often and heal more easily.

Most spontaneously occurring bone problems first appear 3 to 12 months after irradiation; those that occur after trauma (usually dental extraction) are related in time to the traumatic event.

The mylohyoid ridge, which is normally prominent and covered by a thin gingival mucosa, and the anterior arch of the mandible are frequent sites of bone exposure. In some patients, bone exposure over the mylohyoid ridge is seen after dental extractions before irradiation, due to too-tight mucosal closure that stretches and thins the overlying mucosa. Most cases heal promptly, resulting in no significant delay of irradiation. If delayed healing occurs, irradiation must sometimes begin despite the exposure; usually healing continues during the irradiation. Exposure on the anterior arch of the mandible has become less common in recent years at our own institution as a result of greater emphasis on primary surgery, as opposed to irradiation, for most cases of oral cavity cancer. Posterior exposures, at the angle or ascending ramus of the mandible, sites that are well covered by muscle, are rare. If posterior necrosis does occur, it may result in severe infection and trismus.[48]

Although patients who have been edentulous for many years are still at risk of developing mandibular necrosis, overall risk is significantly less than in dentulous patients. A policy of selected tooth removal reduces the risk of necrosis, especially if patients have advanced periodontal disease in the mandibular molars or a history of poor dental compliance.[14] Indiscriminate extraction of all teeth within the treatment volume, however, is not indicated and probably increases the risk of necrosis, particularly in patients with healthy dentition and a history of good dental compliance. After irradiation, extraction of nonrestorable teeth within the high-dose irradiation volume is to be avoided unless all other measures are unsuccessful and patients have severe pain. Many times painful teeth can be successfully treated by root-canal therapy.[15] The risk of postirradiation necrosis is much greater for mandibular than for maxillary extrac-

tions, although delayed healing is not unusual, even in the maxilla. Radiation caries in teeth that are outside the field of irradiation does not predispose patients to osteoradionecrosis since the bone at these sites has not received high-dose radiation; healing is usually normal after extraction.

Marx and coworkers randomly assigned patients who required dental extractions from mandibles that had received high-dose irradiation (6000 cGy 6 months to 15 years before extraction) to receive either penicillin, before and after extraction, or hyperbaric oxygen (HBO) treatment, before and after extraction.[131] HBO treatment consisted of 20 dives at 2.4 atm with 100% humidified oxygen for 90 minutes each session, followed by extraction, then 10 more dives. Thirty-seven patients with 137 wound sockets were treated with penicillin. Thirty-seven patients with 156 wound sockets were treated with HBO. Thirty-one wound sockets (23%) in 11 patients (30%) developed osteoradionecrosis in the antibiotic group and four wound sockets (3%) in two patients (5%) in the HBO group. In addition, the necroses that occurred in the antibiotic group were clinically and radiographically more severe and more often resulted in surgical resection than those occurring in the HBO group.

Occasionally patients have unerupted teeth in the molar area. If well covered, these teeth usually do not cause a problem in the postirradiation period. If a tooth is partially erupted, it generally should be extracted if high-dose irradiation is anticipated.[148] In actual practice, most partially erupted third molars occur in younger patients whose tumors, usually lymphomas, require lesser doses of irradiation so that postirradiation surgery can be accomplished at a later date with little risk. Impacted third molars are not extracted before irradiation, since a prolonged period of healing is required when the bone defect is large.

Destruction of tissue by tumor increases the likelihood of necrosis; patients whose tumors involve the gingiva are at increased risk for bone exposure after irradiation. Patients who continue to smoke and drink after irradiation also are at increased risk. High doses, large treatment volumes, large fractions, and the addition of a radical neck dissection all place patients at greater risk. Patients whose treatment includes an interstitial implant also are more likely to develop necroses. Of 315 patients who received irradiation for carcinomas of the oral cavity, oropharynx, or both at the University of Florida between September 1964 and August 1976, about 5% of the 198 patients whose treatment was by external-beam irradiation alone developed bone necrosis of mild or moderate severity (ie, spontaneous healing in less than 6 months or more than 6 months, respectively); 1% developed severe osteoradionecrosis requiring mandibular resection. Of 117 patients whose treatment consisted of external-beam irradiation and a radium implant, the rate of development of mild or moderately severe necrosis was 18%. Severe necroses occurred in 3%.[159]

MANAGEMENT. In the 1960s, it was common practice to perform mandibulectomies on patients with bone exposure. From experience it is now known that 85% to 90% of bone exposures heal spontaneously after conservative treatment. Even large, moderately severe necrosis may eventually respond to therapy without requiring mandibular resection. Conservative measures often are more successful in cases of osteoradionecrosis induced by denture trauma or preirradiation dental extractions than those occurring after postirradiation extractions, or those which occur spontaneously in association with retained teeth.[15]

The key to treating minor bone exposures is patience. Both patients and physicians must understand that several months are required for healing to occur, and that the area may enlarge before it starts to heal. A number of conservative measures exist to promote healing and to keep patients comfortable. If the bone is rough or protrudes above the level of the gingiva, the oral surgeon files it down to promote healing and to prevent irritation of the tongue. If patients wear dentures, the dentures either should be discontinued or at least should be relieved over the site of exposure to avoid causing further trauma. If the exposure is larger than 1 cm, it is preferable to discontinue the denture until healing is complete.

Surprisingly, most of these patients do not have major discomfort; pain usually is controlled with analgesics such as aspirin and local care. In some patients, continued alcohol ingestion no doubt contributes to the analgesia, although it retards healing. A 2- to 3-week course of antibiotics sometimes reduces discomfort within a few days. A local anesthetic, such as viscous lidocaine applied with a cotton-tipped applicator, helps to control the pain. Under conservative management, most small areas of exposure eventually heal with little or no loss of bone. Local débridement of moderate-sized necroses is done by the oral surgeon when necessary. Small sequestra can be removed in the office. It is not unusual for patients to report that a sequestrum was spontaneously extruded while at home, and when next examined, the area is completely healed.

The late 1970s saw a dramatic increase in the use of HBO for treating osteoradionecrosis and soft tissue necrosis.[44,130,149] Patients treated by HBO at the University of Florida have had close follow-up by an oral surgeon, sometimes on a daily or every-other-day basis, with meticulous local care and frequent débridement until improvement was noted. HBO treatment alone, without an aggressive surgical approach, has been shown to arrest, but often not completely resolve, the process. Since 1983, an HBO program similar to that developed by Marx at Wilford Hall United States Air Force Medical Center in San Antonio, Texas, has been in use at the University of Florida.[130] The protocol does not apply to patients with minor bone exposures, which continue to be treated with less expensive and more conservative approaches, unless the lesion is clearly progressing or causing marked pain. The Wilford Hall protocol consists of three stages:

Stage I: This stage has 30 dives (2.4 atm of 100% oxygen, 90 minutes a day, once a day, 5 days a week), after which patients are reexamined. If the wound shows definite clinical improvement, such as a decrease in the amount of exposed bone, granulation tissue covering the exposed bone, resorption of nonviable bone, and absence of inflammation, patients complete a full course of 60 dives to achieve full mucosal cover. If no clinical improvement occurs by 30 dives, as evidenced by extended or continued exposure of bone, absence of mucosal proliferation, or presence of inflammation, patients are identified as not responding to stage I, and are advanced to stage II.

Stage II: A transoral alveolar sequestrectomy is accomplished with a primary mucosal closure. HBO dives continue after surgery. If healing progresses

without complication, dives continue up to a total of 60. If dehiscence of the wound occurs, leaving exposed bone, patients are identified as not responding to stage II, and are advanced to stage III. In patients whose initial presentation includes either pathologic fracture, orocutaneous fistula, or radiographic evidence of resorption to the inferior border of the mandible, an initial course of 30 dives is given, and patients directly enter stage III of treatment.

Stage III: After a minimum of 30 dives, patients undergo a resection (transoral approach preferred), the margins of which are determined at the time of surgery by the presence of bleeding bone or by tetracycline fluorescence under ultraviolet light (Wood's lamp). The segments of mandible are stabilized with either extraskeletal pin fixation or maxillomandibular fixation. If oral dehiscence or orocutaneous fistula occurs, deepithelialization and primary closure are done. HBO dives are continued until healthy mucosal closure is evident, or a total of 60 dives is reached. Reconstruction, if it is to be done, is dependent on many variables.

Marx entered 58 patients with *refractory* (after surgery, HBO treatment, or nonsurgical approaches elsewhere) osteoradionecrosis onto his protocol.[130] Eleven had orocutaneous fistulae, 11 had pathologic fractures, and 33 had pain. All 58 cases were successfully treated (resolution of pain, retention or reconstruction of mandibular continuity, restoration of function, with maintenance of an intact mucosa over all bone for 18 months, minimum). Resolution was achieved in stage I in 9 patients (16%), stage II in 8 patients (14%), and in stage III in 41 patients (71%). All 41 of the latter patients had successful reconstructive therapy. Marx concluded that HBO treatment alone for refractory cases was rarely (16%) successful because HBO treatment cannot resurrect dead bone. Eighty-five percent required some surgical removal of bone. He concluded, furthermore, that HBO treatment should play an increased role in the management of osteoradionecrosis, with antibiotics, local wound care, and irrigation as adjuncts.

Temporal Bone Necrosis

Osteoradionecrosis of the temporal bone is an unusual complication that may occur after high-dose irradiation of carcinomas of the middle ear, auditory canal, or mastoid, or after incidental irradiation to the normal external auditory canal and temporal bone (eg, in treating nasopharynx or parotid tumors).

Ramsden collected 29 cases of osteoradionecrosis of the temporal bone from four large medical centers over a 30-year period.[170] Two main patterns of necrosis, *localized* and *diffuse*, were observed. The localized form was the most common (18 patients) and usually resulted from incidental irradiation that was directed at primary lesions at some distance from the ear. The most common finding was an area of exposed or dead bone in the external auditory meatus, usually in the floor or anterior wall (Fig. 13-4). Most patients complained of mild otalgia and offensive otorrhea. Sequestration was sometimes present on tomography. Conservative treatment (regular washing, ear drops, and analgesics) usually resulted in gradual separation of the sequestration after 1 to 4 years, after which healing occurred.

Patients with diffuse osteoradionecrosis (11 patients) had extensive involvement of a large part or all of the

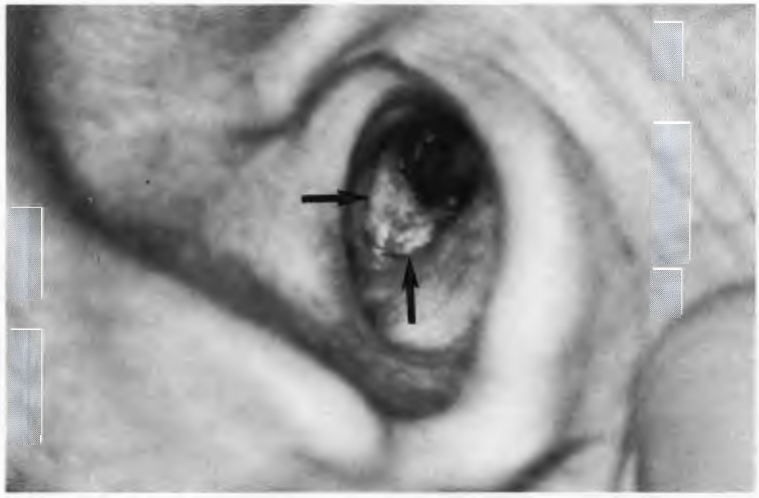


Figure 13-4. Osteoradionecrosis of external auditory canal in a 55-year-old woman 3½ years after superficial parotidectomy and postoperative irradiation of an adenoid cystic carcinoma of the parotid gland. Examination of the resected specimen revealed positive margins and extensive perineural spread. The dose to the temporal bone was 6850 cGy in 32 fractions by a continuous course. At 3½ years, the patient complained of pain and drainage from the right ear. There was exposed bone on the inferior and posterior walls of the external auditory canal (*arrows*). Infection and pain were controlled for several years with antibiotics, although the bone exposure persisted. At 8 years, the patient had increasingly severe pain. CT revealed an erosive process of the mastoid and adjacent squamous portion of the temporal bone. CT-directed biopsy revealed no tumor. The patient was treated with antibiotics and a short course of hyperbaric oxygen therapy. Acute symptoms resolved. The patient continued to have occasional discharge and intermittent pain.

temporal bone. In 10 of the 11 patients, the radiotherapy was directed primarily at the temporal bone, middle ear, or skin of the external meatus, pinna, or temporal region. Patients experienced severe, boring pain with profuse, pulsatile, and offensive otorrhea. Severe intracranial infection occurred in four patients (temporal lobe, cerebellar, or posterior fossa abscesses). Several patients developed other severe sequelae (trismus, cranial nerve palsies, dead ear, vertigo, or death). Treatment required an aggressive surgical approach.

Most reported cases of temporal bone osteoradionecrosis occur 5 years or more after irradiation.[119,170,180,203,217] In Ramsden's series, 11 of 29 cases occurred 10 years or more after irradiation.[170]

Temporal bone necrosis usually is related to technical factors in the treatment. Orthovoltage irradiation, with its high bone absorption, increases the risk. Total dose and fraction size are important; complications in patients of Wang and Doppke all occurred after temporal bone doses calculated to be greater than or equal to 7600 cGy at 200 cGy per fraction with megavoltage apparatus.[209]

MANAGEMENT. In some cases, local treatment (local cleansing, antibiotics, and surgical débridement) is successful, but in other patients a more aggressive approach, including extensive débridement, exploration of the mastoid, partial temporal bone resection, and abscess evacuation, is required. Moderately severe and severe problems also are treated with HBO.

Soft Tissue Necrosis

Atrophy of the mucosa and its supporting stroma, reduced tissue vascularity, and tissue destruction by tumor all predispose patients to soft tissue necrosis. The risk of necrosis is increased by continued alcohol and tobacco consumption.

Most cases of pure soft-tissue necrosis occur within 2 years. Soft tissue necrosis in association with bone exposure may occur at any time. After interstitial therapy, most cases of necrosis appear within 5 to 8 months. Occurrence after 2 years generally is preceded by trauma to the mucosa.

Soft tissue necroses are most common after irradiation of lesions within the oral cavity or oropharynx; they are unusual after treatment of cancer of the nasopharynx and larynx, but occasionally are seen after successful irradiation of cancer of the posterior pharyngeal wall. Extremely rapid tumor dissolution (as sometimes occurs in patients who receive pure accelerated fractionation, eg, 160 to 200 cGy, three times each day) in patients whose tumors involve the lateral pharyngeal wall may result in carotid artery exposure and fatal hemorrhage.[90] Necrosis is related to fraction size, total dose, volume, and use of interstitial treatment. Of 315 patients with squamous cell cancer of the oral cavity or oropharynx who received radical irradiation at the University of Florida between 1964 and 1976, mild (spontaneously healed within 6 months) or moderately severe (spontaneously healed, but required longer than 6 months) soft tissue necroses were observed in about 10% of patients after external-beam irradiation alone, and in about 20% of those who received a combination of external-beam and interstitial irradiation; severe soft tissue necroses (requiring an operation or prolonged hospitalization) were rare, occurring in 1 of 198 patients (0.5%) treated by external-beam therapy alone and 1 of 117 (1%) after external-beam plus interstitial irradiation.[159]

MANAGEMENT. Necrosis must first be distinguished from recurrent cancer. Although both conditions frequently ulcerate the mucosa, some clinical parameters can help to distinguish between the two. Recurrence of the primary cancer after irradiation almost always occurs at the center of the initial lesion. Ulceration outside the original cancer area usually is due to necrosis. Most cancer ulcers have a rolled margin, as opposed to the nearly flat, more sharply demarcated margins of necrosis. The induration around a tumor recurrence usually is a little more pronounced than around a necrosis. Both kinds of ulcer may enlarge, but a cancer ulcer rarely decreases in size.

If physicians cannot decide whether the ulcer represents tumor recurrence or necrosis, patients are asked to return every 2 weeks for reexamination. If soft tissue necrosis is the most likely cause of the ulcer, biopsy is not performed, since this may cause the necrosis to enlarge. If recurrent tumor is likely, biopsy is mandatory, since the chance to perform surgical salvage is lost if one procrastinates too long. *It is better to err on the side of biopsy when doubt exists.* Our rate of success in the clinical diagnosis of necrosis versus recurrence is only fair, about 70%. In some areas, particularly the tongue, biopsy may have to be done under anesthesia, since a deep biopsy is necessary to show recurrence. Negative biopsy results should be viewed with suspicion if there is a strong likelihood of recurrence, and repeat biopsies are in order.

The management of soft tissue necrosis depends on the site involved and the severity of pain produced. Tiny necroses may be asymptomatic, but in certain sites (eg, the lateral tongue or floor of the mouth) even a 1- to 2-mm superficial ulcer may be painful. A topical anesthetic such as viscous lidocaine, 2%, may make patients comfortable enough to eat normally. Antibiotics such as tetracycline hydrochloride, 250 mg orally four times a day, often produce dramatic relief of pain, particularly when the ulceration is deep and infected. It is essential that patients discontinue using alcohol and tobacco. If the area of necrosis is constantly traumatized by dentures, they should not be worn until healing has occurred. More than 95% of soft tissue necroses heal with conservative treatment, although several months and great patience on the part of both physician and patient are required. Cases that fail to respond to more conservative means may benefit from a course of HBO. Once healing has occurred, the scar appears pale and thin, and often is slightly depressed below the level of the surrounding mucosa; reappearance of necrosis at the same site is unusual.

Dion and coworkers have used pentoxifylline (400 mg three times a day) to treat soft tissue necrosis.[51]

Cartilage Necrosis

In early life, cartilage has no blood vessels and contains a large amount of interstitial substance with only a few cells of low mitotic activity. In later life, the thyroid, cricoid, and arytenoid cartilages become ossified and develop a central marrow cavity with hemopoietic and adipose tissue and a blood supply.[137] Ossification occurs earlier and more completely in men than in women. The epiglottis, which is primarily elastic cartilage, only occa-

sionally develops a small plaque of calcification. Numerous normal cartilaginous structures in the head and neck area, including the larynx, trachea, external ear, eustachian tube, and nose, are incidentally or intentionally irradiated to a high dose. The often-voiced fear of cartilage necrosis arose from the orthovoltage era, when vocal cord and skin cancer were treated with large daily fractions; cartilage necrosis then was a constant worry of therapists. It is now known that cartilage that is covered by a normal mucous membrane or skin usually tolerates conventionally fractionated high-dose irradiation. Although cartilage that has been compromised by tumor invasion, infection, or prior surgery is more vulnerable to radiation injury, these conditions themselves constitute no contraindication to irradiation, since the risk of cartilage necrosis still is low. At the University of Florida, there have been numerous uncomplicated cures after irradiation of moderately advanced cancer of the suprahyoid and infrahyoid epiglottis (see Chap. 18), nose (see Chap. 22), and skin (see Chap. 25) in which cartilage invasion was present.

Chondronecrosis generally occurs within the first posttreatment year, but can be precipitated by trauma many years after treatment. Biopsies are sometimes the precipitating cause and should *not* be done after irradiation unless recurrence is suspected.[2,163] Cartilage necrosis often starts with necrosis of the soft tissues (skin or mucous membrane) overlying the cartilage.

Laryngeal Chondronecrosis

Chondronecrosis of the larynx is rare, occurring in about 1% of patients who receive doses in the range of 6000 to 7000 cGy at 200 cGy per fraction. For T1–2 vocal cord cancer treated at the University of Florida (1964 through 1984) with 225-cGy fractions, the incidence of necrosis or severe edema, according to dose, was as follows: 5400 to 5700 cGy (mostly 5625 cGy), 0 of 33; 6000 to 6500 cGy (mostly 6300 cGy), 1 of 141 (0.7%); and for 6700 to 7000 cGy (mostly 6750 cGy), 2 of 7 (29%).[135] The risk increases with larger daily fractions (Table 13-1)[28,67,83,99,198] and larger treatment volumes; the risk is greater for supraglottic than for vocal cord carcinoma. For patients with cancer of the oral cavity, oropharynx, or nasopharynx, the entire larynx should not be included in the treatment portals.[134] Cartilage that has been compromised by partial laryngectomy seems likely to develop necrosis after irradiation, but in practice it is rarely seen. Patients who continue to smoke or drink alcohol after treatment are at increased risk.

The symptoms and signs of cartilage necrosis (hoarseness, pain, edema, shortness of breath, tenderness over the cartilage, and foul breath) mimic those of recurrent cancer. Aspiration pneumonia, lung abscess, or laryngocutaneous fistula may result. Since most necroses and many recurrences occur within 1 year after treatment, time to onset is not helpful in distinguishing the two. Tumor recurrence is many times more common than cartilage necrosis; nevertheless, a strong suspicion of recurrence should exist before biopsy is undertaken. If patients have pain and marked edema, with or without obvious tumor regrowth, CT scan is performed for confirmation of the findings. If an obvious focal abnormality is noted on CT scan, then direct laryngoscopy and biopsy are indicated. If only edema but no focal abnormality is noted on CT scan, and no evidence of disease is noted at direct laryngoscopy, blind biopsies should *not* be performed, as they may precipitate a chondronecrosis. In instances where patients have no pain, only moderate edema, an adequate airway, and CT scans showing no focal lesions, clinical follow-up alone is indicated. Even deep biopsy may fail to obtain representative tissue in some recurrent cancers. Tracheotomy may be necessary for aspiration or edema. Antibiotic therapy is begun, and nasogastric or gastrostomy alimentation may be necessary. HBO therapy has been reported to be effective in the management of chondronecrosis. Ferguson and coworkers reported on eight patients who developed laryngeal chondronecrosis within 15 months of completing irradiation.[64] One patient had a laryngocutaneous fistula, three had undergone tracheostomy, and the other four had severe pain, dysphagia, or tenderness over the cartilage. Patients received 40 dives (2 atm of 100% oxygen, 2 hours each, 6 days a week) plus antibiotics and humidity. Signs and symptoms of necrosis were dramatically relieved in seven patients; one patient required laryngectomy.

Conservative measures sometimes are successful in resolving the necrosis (see Chap. 18, Fig. 18-42). If conservative measures are unsuccessful, laryngectomy is recommended because the problem is more apt to be tumor recurrence than necrosis.

Chondronecrosis of the Nose and Ear

In treating cancer of the nasal cavity and paranasal sinuses, the normal nasal alae frequently receive 7000 cGy over 7 weeks; at the University of Florida, no chondronecrosis has been observed in this patient group. Skin cancer on the nose or ear also requires high-dose cartilage irradiation. Even when such lesions invade cartilage, necrosis is rare after conventionally fractionated

TABLE 13-1. Chondronecrosis After Irradiation of Laryngeal Cancer: Time–Dose Relationship

Study	Primary Site	Tumor Dose	Fraction Size (cGy)	Patients	Patients With Necrosis
University of Florida[135]	Glottis (T1–2)	5400–6525 cGy/4½–6 wk	225	174	1 (0.6%)
Princess Margaret Hospital[83]	Glottis (T1)	5500 cGy/5 wk	210–230	283	0
M. D. Anderson Hospital[67]	Glottis and supraglottis	6000–7000 cGy/5½–7 wk	200–225	503	6 (1%)
Rush Presbyterian-St. Lukes[99]	Glottis (T1–2)	6500 cGy/5–5½ wk	225–250	135	1 (0.7%)
Liverpool[198]	Glottis and supraglottis	5500 cGy/3 wk	344	129	9 (7%)
Penrose[28]	Glottis (T1–2)	6100–6600 cGy/3½–4 wk	~300	16	1 (6%)

therapy (see Chaps. 22 and 25).[49,157] If necrosis does occur, it requires débridement and grafting.

Skin and Subcutaneous Tissues

Skin

Since modern radiation therapy is conducted with supervoltage equipment, severe late skin changes are infrequent. Today, the only common indication for orthovoltage irradiation is skin cancer. After orthovoltage treatment, usually epidermal atrophy and sometimes telangiectasis occur. The skin is hairless and dry because the sweat and sebaceous glands cease to function. Some patients need to apply petrolatum regularly to keep the skin pliable and to prevent fissures from occurring. Acne does not occur in the irradiated field. Pigment changes also may occur; after high-dose treatment, a thin, achromic, and telangiectatic scar develops. Achromia results from melanocyte destruction; such areas readily sunburn. In some patients, "tanning" or hyperpigmentation may persist; in the author's experience, this has been observed most commonly in darkly pigmented patients (one Oriental, one black) who received postoperative high-dose electron treatment for sarcomas of the central face. If the skin is severely damaged, it may ulcerate, especially after trauma; sometimes grafting is required. With the regimens outlined in Chapter 25, skin necrosis after initial healing has not been seen.

Subcutaneous Fibrosis

Although skin injury is rarely a major problem, late effects on subcutaneous tissues still are important. Subcutaneous fibrosis usually appears within 6 to 12 months after treatment and is slowly progressive. Decreased pliability of the subcutaneous tissues exists. In severe cases, the tissues may have a woody texture and become fixed into a single hard mass in which the subcutaneous tissue is not separable from overlying skin or underlying muscle or bone. If the radiation entered the patient tangential to the skin, then skin and subcutaneous changes occur simultaneously. Patients with a great amount of adipose tissue in the subcutaneous layer tend to develop the most severe changes. Fibrosis is rarely painful.

After high-dose treatment of vocal cord cancer with a single, ipsilateral 4 × 4–cm to 5 × 5–cm field, the only change is an unsightly puckered area with subcutaneous plaque-like thickening in the center of the field. The thickened area occasionally is confused with an enlarged lymph node by the inexperienced clinician. Lesser subcutaneous changes are noted in the anterior half of the field and in the anterior midline. When parallel-opposed ^{60}Co portals are used to treat vocal cord cancer, lesser degrees of subcutaneous fibrosis are seen.

Large areas of fibrosis may be accompanied by a tight, constrictive sensation. Obstructive lymphedema may be associated with fibrosis and may produce intermittent episodes of erysipelas.

High-dose irradiation of metastatic lymphadenopathy results in more subcutaneous fibrosis in the neck than does a comparable dose to a neck that has no palpable adenopathy; apparently, the fibrous stroma that replaces the tumor mass contributes to the reaction. Large daily fractions also increase the risk of subcutaneous fibrosis. Although fat necrosis is a potential risk after high-dose irradiation, the condition is rare.

Pharyngeal Stenosis

A rarely observed complication of high-dose irradiation consists of progressive fibrosis and eventual stenosis of the supraglottic larynx or pharynx, leading to severe dysphagia, aspiration, or airway problems. The complication has been observed in two patients from the University of Florida (one received a portion of her treatment at another institution before referral to the University of Florida), requiring tracheostomy in one and resulting in several episodes of aspiration pneumonia in the other.

Wound Healing

Wound healing is a complex, dynamic process involving an initial inflammatory-type response to tissue injury followed by proliferation of epithelial and endothelial cells, fibroblasts, and capillaries and later by synthesis, secretion, and eventually restructuring of collagen by fibroblasts.[142] Maximal mechanical wound strength is not attained for months, or even a year or more, after surgery. Irradiation can interrupt or delay the healing process at several points, especially at those points that depend on normal cell proliferation.[142]

Planned Preoperative Irradiation

A number of authors have performed animal experiments to study the effects of irradiation administered before wounding on (1) delay of gain in tensile strength[53,76,111,140,150,195,218]; (2) time to complete wound closure[169]; (3) histologic progression of collagenesis[4,53,111,194]; and (4) incidence of postoperative wound infection.[5] The experiments studied the effects of various doses, usually administered as single fractions, given at various intervals before surgery. Whereas not all studies produced identical findings, most investigators agreed on the following:

1. Irradiation produces delays in complete healing and tensile strength. The greatest delays occur when irradiation immediately precedes wounding, or when it is administered less than 1 week before surgery. Delaying surgery beyond 3 weeks provides little additional advantage in terms of tensile strength.
2. The effect of irradiation on wound healing is dose related. Fractionated irradiation produces significant sparing in terms of wound strength with an α/β ratio of 250 cGy, typical of a late-responding tissue.[77]
3. The delay in tensile strength appears to be caused by delayed collagen synthesis, probably due to depletion of fibroblasts.
4. Preoperatively irradiated wounds are more susceptible to bacterial infection than nonirradiated wounds. The risk increases with dose and is particularly significant if the operative bed includes bacterial contaminants (as occurs when the aerodigestive tract is breached).
5. Once healing is complete, the scar is morphologically normal and final wound strength is the same as in unirradiated controls.

Although no evidence exists that delaying surgery beyond 3 weeks benefits tensile strength, frequently other practical considerations make longer delays (eg, 4 to 6

weeks) desirable, such as allowing time for mucositis to resolve, a positive nutritional state to be restored, and fixed nodal masses to shrink away from the carotid artery and base of skull.

Salvage Surgery

Chronic radiation effects result in tissues that are fibrotic, hypoxic, and susceptible to infection. Once these changes have occurred, they are not reversible and do not improve with time.[140] The doses that have been administered to the tissues before salvage surgery usually are 6000 to 7500 cGy. Both the high doses and existing fibrosis lead to a rate of complications that is higher than in planned preoperative irradiation cases.[169] Morbidity is increased by the same factors that increase late complications in general, namely, high total dose, large dose per fraction, large field size, and surgical procedures of great magnitude. Longer intervals to surgery and split-course irradiation techniques do not reduce the risk of complications.[93] Complications, when they occur, tend to be more severe in heavily irradiated patients than in unirradiated patients, leading to increased rates of fistulization, prolonged hospitalization, and carotid exposure.[94]

Planned Postoperative Irradiation

High doses administered immediately or within several days postoperatively significantly delay wound healing.[53,76] If sufficient time (usually several weeks) has elapsed between surgery and irradiation, irradiation has no detectable effects on healing.[140] Occasionally, a patient in need of postoperative irradiation has an open, slow-healing wound, and a decision must be made either to delay treatment and risk tumor recurrence or to proceed with irradiation and risk greater wound complications. In general, if the area of incomplete wound closure is not extensive and does not overlay a vital structure (eg, the carotid artery), irradiation is started at about 6 weeks. If the wound overlies the carotid artery, further delays are necessary, and the exact timing of irradiation must be individualized.[92]

Visual Apparatus

The eye is an externalized portion of the brain. The neural retina is a derivative and extension of the diencephalon, and the optic nerve is structurally and functionally a tract of the central nervous system (CNS), rather than a peripheral nerve. The clear, aqueous fluid within the eye more closely resembles cerebrospinal fluid than any other body fluid, and the blood vessels of the retina are like those of the brain.[34]

Although primary tumors of the eye (eg, melanoma, retinoblastoma) and optic nerve (eg, glioma) are rare, tumors that involve tissues adjacent to these structures are relatively common. Because many of these tumors are best treated with irradiation, the visual apparatus frequently receives incidental irradiation. Tumors for which irradiation usually is employed include those of the nasal cavity and paranasal sinuses, nasopharynx, orbit (eg, lymphomas), and CNS (eg, pituitary), as well as advanced cancer of the eyelid and periorbital skin. In a recent analysis at the University of Florida of a series of patients with tumors arising in the nasal cavity, ethmoid sinus, or sphenoid sinus, almost half of patients had evidence of direct orbital invasion; in 20% of patients, the invasion was of such a degree as to produce exophthalmos, blindness, or a palpable orbital mass.[162] Irradiation of the eye and optic nerve produces a variety of clinical problems.

The Eye

When treating tumors of the paranasal sinuses with irradiation, varying portions of the eye are in the fields of treatment, depending on the degree to which the orbit is invaded.[161]

When *orbital invasion is extensive,* all of the orbital contents are irradiated, including the eyeball and all of the lacrimal tissue (Fig. 13-5*A*). If the administered dose is high, as when treating a carcinoma, a dry eye results and visual loss usually occurs within 6 to 10 months after treatment, due to degeneration of the anterior segment of the eye, with resultant corneal ulceration and opacification. The direct effects of irradiation on the cornea also contribute to the problem. Lower doses, as used when treating lymphomas, result in only mild symptoms of a dry eye and cataract formation, usually a correctable form of visual loss.

If *orbital invasion is limited* so that most of the lacrimal tissue can be spared high-dose irradiation (see Fig. 13-5*B* and *C*), severe dry-eye problems do not occur, even when high doses are administered. If the dose to the eyeball itself has been high, however, visual loss due to posterior segment degeneration, radiation retinopathy, occurs, usually after a 2- to 3-year latency period. If low total doses are used, patients usually remain asymptomatic in the follow-up period with regard to dry eye complaints and retinal problems, but still are at risk for cataract formation if the lens was irradiated.

Even when *no orbital invasion is present,* it is often necessary to include a portion of the contiguous orbit and the medial one fourth to one third of the eyeball in the irradiation field (see Fig. 13-5*D*) because of the anatomic configuration of the sinuses, and because of possible subclinical disease extensions through the thin bony walls that separate the sinuses from the orbit. Although visual loss secondary to eyeball injury is rare in this setting, a risk of blindness due to optic nerve injury still exists, usually after a 1- to 6-year latency period; the risk depends on the daily fraction size and total dose administered.

Patients who are to undergo high-dose eye or optic nerve irradiation should be evaluated before irradiation by an ophthalmologist knowledgeable in radiation complications. Most potential visual complications can be anticipated during the treatment-planning stage, and patients should understand these risks. Continued follow-up in the posttreatment period should be on a regularly scheduled basis of prophylaxis, not just when indicated by specific problems. Frequently, a number of ophthalmologic problems occur simultaneously (eg, dry-eye symptoms, cataracts, radiation retinopathy, and glaucoma), which makes assessment confusing and management difficult. Before undertaking any specific treatment, the ophthalmologist should correlate the treatment details with the radiation therapist, since some pitfalls may be avoided by good communication. For example, if high-dose irradiation has been administered to the eyeball, cataract extraction should not be followed by prosthetic lens implantation, since the complication

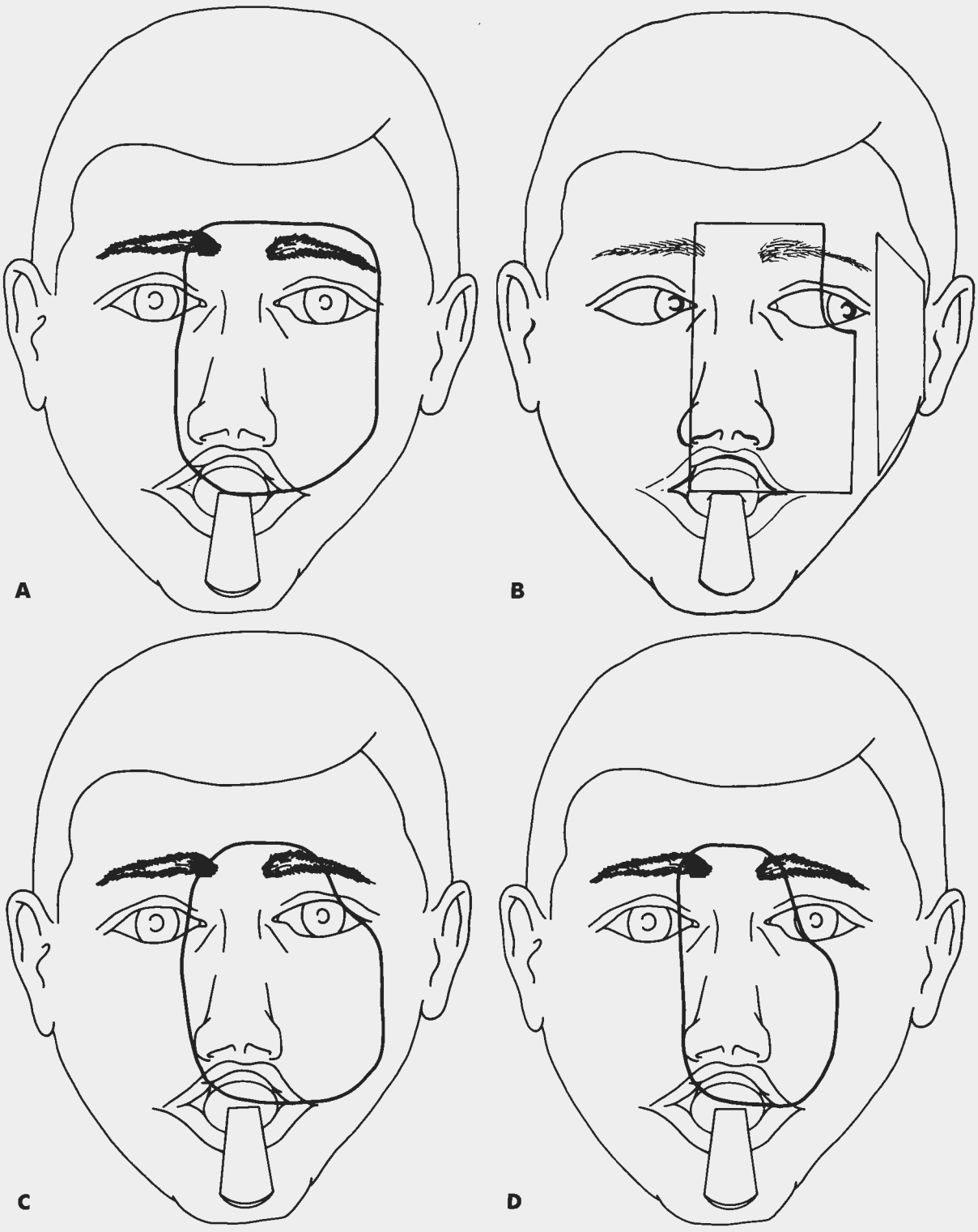


Figure 13-5. Anterior portals used to treat tumors of nasal cavity and paranasal sinuses. (*A*) Extensive orbital invasion (eg, palpable orbital mass, proptosis, or blindness). No lacrimal shielding. (*B*) Limited orbital invasion present. The major lacrimal gland is shielded. Patient is instructed to gaze laterally to displace lens from portal. This technique was discontinued at the University of Florida after 1970. (*C*) Limited orbital invasion present. The major lacrimal gland is shielded. This technique has been used at the University of Florida since 1971. (*D*) No orbital invasion. (*A*, *C*, and *D* from Parsons JT, Mendenhall WM, Bova FJ, Million RR. Head and neck cancer. In: Levitt SH, Khan FM, Potish RA, eds. Levitt and Tapley's Technological basis of radiation therapy: practical clinical applications, ed 2. Philadelphia, Lea & Febiger, 1992:225; *B* from Parsons JT, Fitzgerald CR, Hood CI, Ellingwood KE, Bova FJ, Million RR. The effects of irradiation on the eye and optic nerve. Int J Radiat Oncol Biol Phys 1983;9:610; copyright © 1983, Pergamon Press)

rate is increased and the expected benefits would be negligible, since patients will almost certainly develop radiation retinopathy. Anterior-segment disease should be treated early and aggressively to avoid corneal complications. Even when vision is lost, vigorous attempts to save the eye are worthwhile for cosmetic reasons.

The University of Florida data are based on observations made in 74 patients who received irradiation to the eye, optic nerve, or both with 2-MV x-rays or ^{60}Co for tumors of the orbit, paranasal sinuses, nasopharynx, or eyeball between October 1964 and March 1979.[160] Dose calculations were made at each area of interest.

Dose to the lacrimal apparatus, for patients whose major lacrimal gland was in the treatment portal, was calculated at a depth of 1 cm from the anterior skin surface, because this is the approximate depth of the major lacrimal gland.

Retinal doses were calculated only for patients in whom half or more of the posterior pole of the eye was encompassed by the high-dose region. For a variety of reasons (including portal arrangement, penumbra, and field reductions), the distribution of dose across the retina often was inhomogeneous. The specified dose is the minimum dose received by most of the retina (Fig. 13-6).[158]

Optic nerve dose was specified as the maximum dose to any portion of the nerve. The specification of maximum dose rather than minimum dose was necessary because in many instances a portion of the optic nerve was outside the field of irradiation altogether, so the minimum dose would have been quite low. The inconsistency in specifying the retinal dose as a *minimum* dose to most of the retina and the optic nerve dose as a *maximum* anywhere along the nerve is justifiable, because the retina apparently is capable of tolerating high doses to small volumes,[23,196] whereas the optic nerve is not.[45,69,101]

Lacrimal Apparatus

THE LACRIMAL GLANDS. The tears are composed of secretions from the following:

- Major lacrimal gland, which is in proximity to the globe in the superior temporal quadrant of the orbit
- Accessory lacrimal glands of Krause, which are located in the conjunctival fornices, mainly the superior fornix
- Accessory lacrimal glands of Wolfring, which are located at the superior margin of the upper tarsal plate
- Sebaceous meibomian glands, which are somewhat more plentiful in the upper than the lower lid
- Accessory sebaceous glands of Zeis and the glands of Moll, which lie near the lid margins
- Goblet cells, which are distributed throughout the conjunctiva

Although their mass is small in relation to the major lacrimal gland, the accessory lacrimal glands are believed to be responsible for the basal secretion of tears (Fig. 13-7).[179] Reflex secretion is from the main lacrimal gland.[96]

Under normal conditions, the tears form a thin layer that wets, lubricates, and flushes the corneal and conjunctival surfaces and tends to improve the optical properties of the cornea by smoothing any existing surface irregularities. The fluid flows to the lacrimal puncta, especially the lower one, then through the canaliculi, lacrimal sac, nasolacrimal duct, and into the nose beneath the inferior turbinate. The tear film consists of three layers:

- Superficial lipid layer, derived from meibomian and Zeis gland secretions, which helps retard evaporation
- Middle aqueous layer, produced by the major and accessory lacrimal glands
- Deep mucinous layer, which serves to wet the relatively hydrophobic corneal and conjunctival epithelia, produced by conjunctival goblet cells.

Deficiency of any of the three components leads to a loss of tear-film stability, with the result being dry spots due to rapid breakup of the tear film (Fig. 13-8). A dry eye is the result, and this, in turn, leads to damage of the conjunctival and corneal epithelium (keratoconjunctivitis sicca). Because the corneal epithelium is endowed with numerous nerves, pain from a dry eye often is marked. Corneal epithelial defects may be readily viewed by staining with fluorescein.

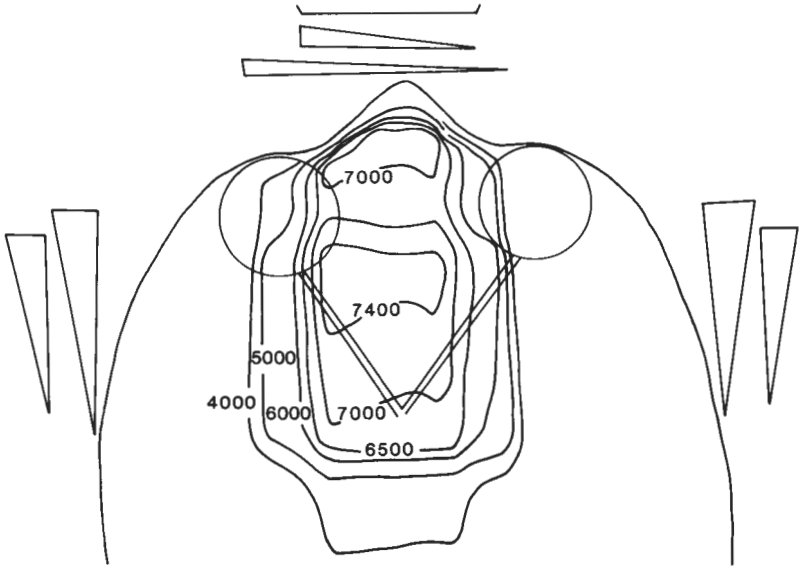
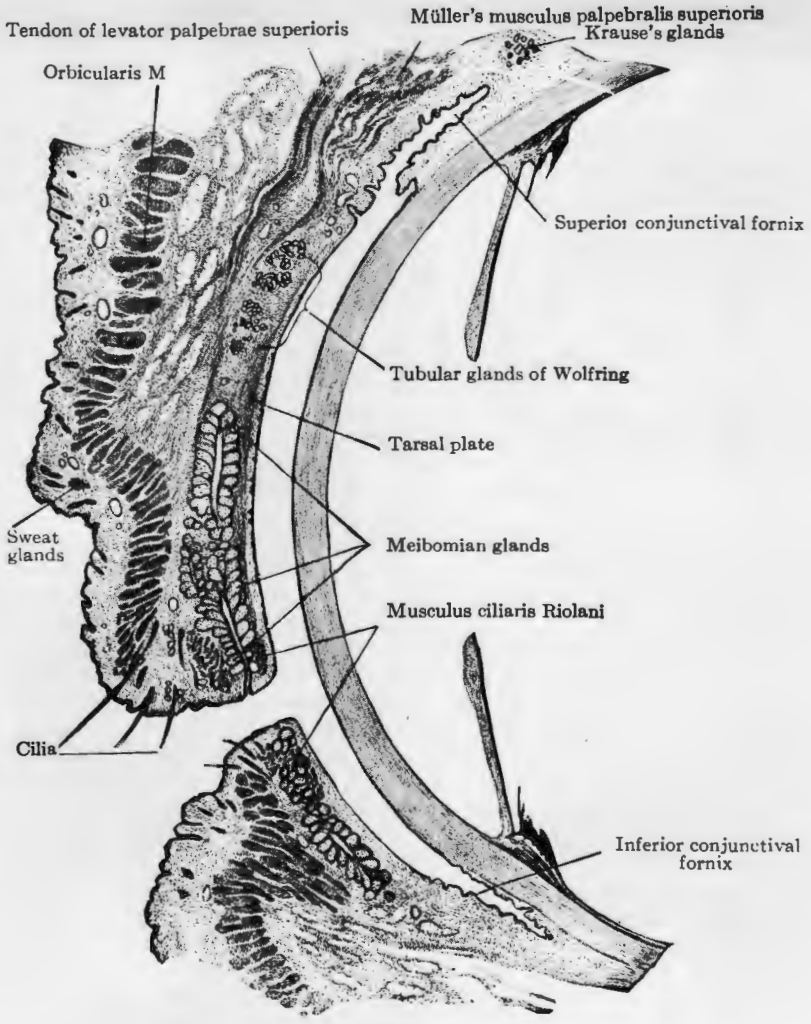


Figure 13-6. Isodose distribution from anterior and two lateral wedge fields used to treat a neurofibrosarcoma of the left nasal cavity. The anterior field was reduced twice, and the lateral fields were reduced once. Because of penumbra, portal reductions, and the multifield technique, the dose to the left retina was quite inhomogeneous. For purposes of calculation, the left retina is said to have received 5000 cGy, but it is recognized that the dose to a small portion of the temporal retina was less than 1000 cGy, whereas nasally a small segment received 7000 cGy. (From Parsons JT, Bova FJ, Fitzgerald CR, Hood I, Mendenhall WM, Million RR. Tolerance of the visual apparatus to conventional therapeutic irradiation. In: Gutin PH, Leibel SA, Sheline GE, eds. Radiation injury to the nervous system. New York, Raven Press, 1991:286)

Figure 13-7. Sagittal section through the eyelids and eyeball. Note the location of the accessory lacrimal glands of Krause in the superior conjunctival fornix and the accessory lacrimal glands of Wolfring at the superior margin of the tarsal plate. (Scheie HG, Albert DM. Textbook of ophthalmology, ed 9. Philadelphia, WB Saunders, 1977:50)



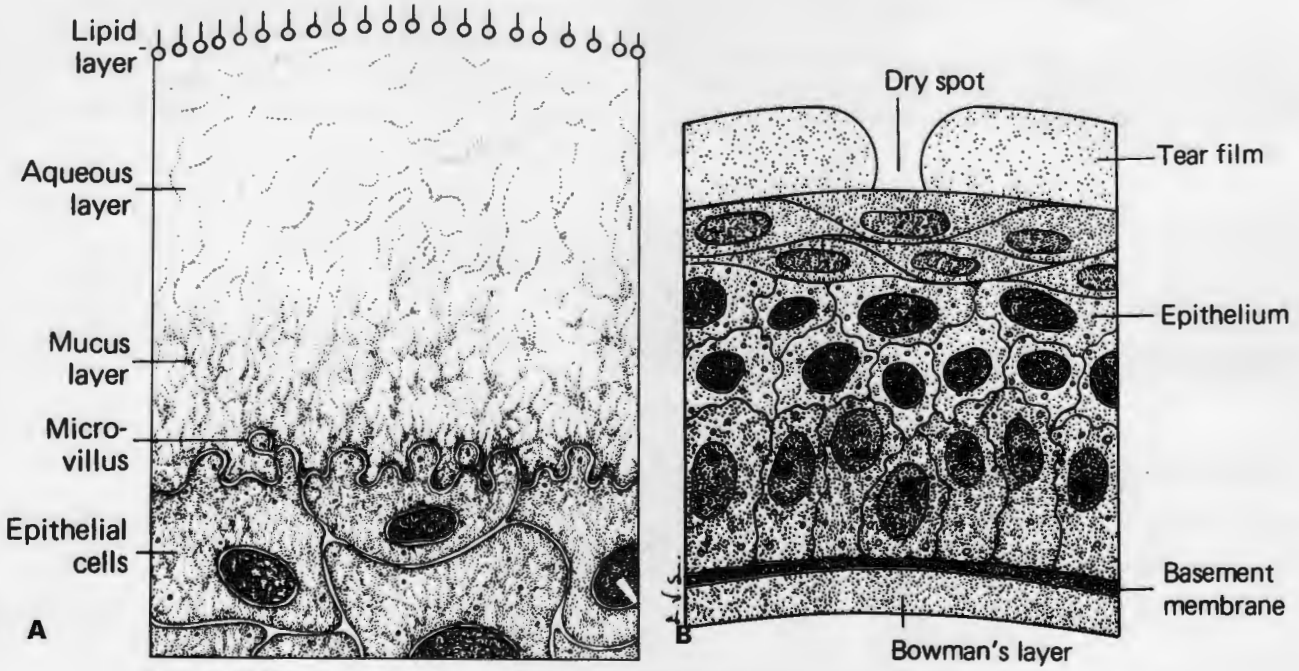


Figure 13-8. (*A*) The three layers of the ocular tear film, shown here covering the superficial corneal epithelium. (*B*) Loss of normal constituents of the tear film leads to rapid tear film breakup, with resultant dry spots that expose the corneal epithelium and lead to damage of its cells. (From Tabbara KF. Tears. In: Vaughan D, Asbury T, Tabbara KF, eds. General ophthalmology, ed 12. East Norwalk, CT, Appleton & Lange, 1989:68 and 70)

In a histopathologic study of eight eyes that were removed 5 days to 16 years after irradiation (which, in most cases, was with ^{60}Co for tumors of the paranasal sinuses), Karp and colleagues demonstrated diffuse involutional atrophy of the meibomian glands in all eight specimens. In three eyes, there was total loss of meibomian glands and ducts, and in six, no accessory lacrimal tissue could be identified.[97] In one patient whose entire lacrimal gland was available for study, the gland was diffusely atrophic. In three of seven specimens where it could be determined, the sebaceous glands of Zeis were absent. Although the glands of Moll could usually be identified, they were frequently atypical.

Since most of the basal secretion of tears comes from the accessory lacrimal glands, which are most plentiful in the upper lid and superior conjunctival fornix, efforts always should be made to shield some of the upper lid, in addition to the major lacrimal gland. Because tumors most frequently invade the orbit through its floor (maxillary sinus) or medial wall (ethmoid sinus), the superolateral orbit usually can be shielded (Fig. 13-9), unless orbital invasion is extensive. During treatment, the eye is locally anesthetized and a lid retractor is inserted so that part of the upper lateral eyelid is displaced from the treatment field; maintaining the open-eye position during treatment also prevents bolus effect by the lids on the cornea and conjunctiva.

When the orbit is extensively invaded by carcinoma, high-dose irradiation of the entire orbit is necessary, and generally results in severe dry-eye syndrome. If the dose to the entire eye and lacrimal tissue exceeds 5000 cGy, prospects of maintaining vision are poor. Patients develop a red, painful, scratchy eye (foreign-body sensation) and photophobia. The drying effects of wind are particularly bothersome. Although most patients from the University of Florida with severe dry-eye syndrome had moderate to severe pain, two had little pain and little or no conjunctival reaction during the first few posttreatment months, but they eventually lost sight due to corneal injury.

A time–dose scatter distribution for the production of severe dry-eye syndrome (corneal opacification, ulceration, or vascularization sufficient to cause visual loss) is shown in Figure 13-10. Data are included on 20 eyes in 19 patients after irradiation with ^{60}Co or 2-MV x-rays to the entire orbit. Whenever portal reductions were made to exclude the major lacrimal gland, the dose shown is that before reduction. All eyes that received greater than or equal to 5700 cGy had severe keratoconjunctivitis sicca within 1 to 2 months after treatment; frequently, the cornea was opaque by 1 year. Two eyes that were injured after lower doses (3200 and 4500 cGy, respectively) had slowly progressive corneal opacification and vascularization. Enucleation eventually was required at 4 and 8 years, respectively, because of moderately severe symptoms and visual acuity of only "hand motion" in both eyes. Symptoms in uninjured eyes ranged from none to occasional mild photophobia and mild foreign-body sensation.

Although additional data are needed, most patients appear to tolerate doses in the range of 3000 to 4000 cGy (180 cGy per fraction) to the entire orbit with ^{60}Co without developing severe symptoms of a dry eye (Fig. 13-11).[160] These data are in general agreement with those of Bessell and coworkers, who noted disordered ocular lubrication in 0 of 17 patients who received less than 3000 cGy (200 cGy per fraction); 2 (5%) of 43 patients who received doses of 3000 to 3900 cGy; and 3 (23%) of 13 patients who received 4000 to 4900 cGy to the orbit for lymphomas.[13] High-energy x-rays (eg, 17 to 20 MV) spare more of the lacrimal tissue, owing to the buildup characteristics of the beam, but they may create other undesirable technical problems, depending on the distribution of tumor.

In association with corneal ulceration, five patients developed acute anterior uveitis; pain was often severe, sometimes requiring hospitalization and intensive medical management with cycloplegics, mydriatics, narcotic analgesics, tranquilizers, and antibiotic therapy as indicated.[160]

Treatment of a dry eye is symptomatic. For mild or moderate dry-eye syndrome, artificial tears are used during the day and a sterile ophthalmic lubricating ointment is applied at night. Hydrophilic soft contact lenses sometimes are used as a protective bandage for corneal epithelial defects and may serve as a tear reservoir, but

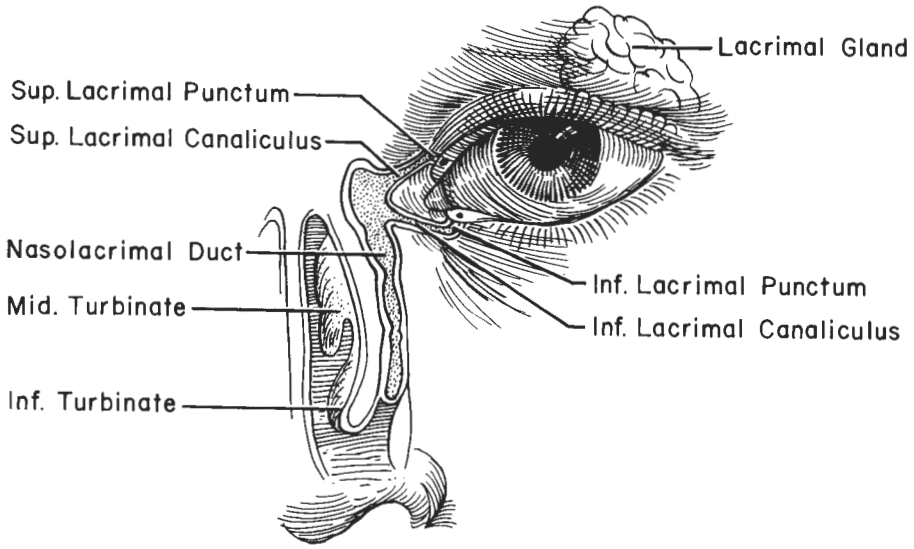


Figure 13-9. The major lacrimal gland and lacrimal drainage system.

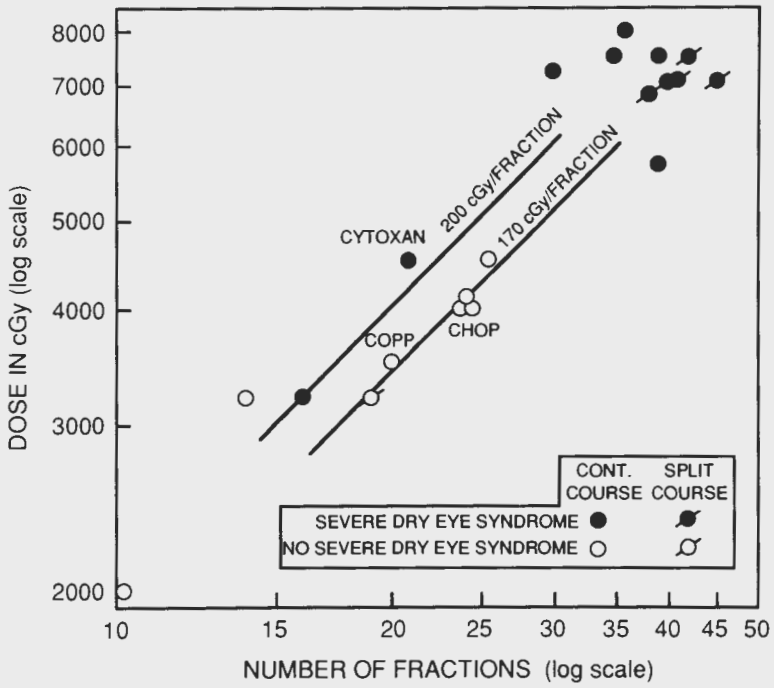


Figure 13-10. Dose to the lacrimal tissue versus the number of fractions for production of severe dry-eye syndrome (corneal opacification, vascularization, or ulceration sufficient to cause visual loss). Included are data on 20 eyes in 19 patients following continuous- or split-course irradiation with cobalt-60 or 2-MV x-rays for a variety of head and neck tumors. The dose to the lacrimal tissue is regarded as the dose at 1-cm depth (ie, at approximately the major lacrimal gland). The exact dose received by the accessory lacrimal tissue in the eyelids is difficult to estimate because the lid is so thin; however, in the eye-open position, which was used in all patients, one would not expect significant sparing of the lacrimal tissue (located mainly in the superior conjunctival fornix and tarsal portion of the upper lid), since it would be bolused by the soft tissues of the orbital portion of the lid. Three patients (four eyes) who received chemotherapy in addition to irradiation are so designated. Length of follow-up on the eight eyes that did not develop severe dry-eye syndrome was 2½ to 12 years (mean 6.2 years, median 5 years). Reference lines have been added for ease of interpretation of the data and represent treatments administered at 170 and 200 cGy per fraction, respectively; they are not isoeffect lines. (Parsons JT, Fitzgerald CR, Hood CI, Ellingwood KE, Bova FJ, Million RR. The effects of irradiation on the eye and optic nerve. Int J Radiat Oncol Biol Phys 1983;9:611, copyright © 1983, Pergamon Press)

they are not always well tolerated by patients who have severely dry eyes due to irradiation; one patient developed a spontaneous corneal perforation while using a soft contact lens over a centrally thinned cornea. In two other patients, a full conjunctival flap was used to cover corneal epithelial defects to control severe pain; pain relief was complete in one, but incomplete in the second patient. In the early stages of dry-eye syndrome, visual acuity is usually only slightly impaired. If severe dry-eye syndrome develops, then corneal stromal edema, clouding, and eventually corneal scarring and vascularization occur. Vision deteriorates rapidly, and the entire eye becomes vulnerable to bacterial infection. Treatment of a painful, nonseeing eye is by evisceration or enucleation.

THE NASOLACRIMAL DRAINAGE SYSTEM. The nasolacrimal duct usually is not affected by high-dose irradiation unless it has been disrupted by tumor or prior surgery. Only one patient at the University of Florida is known to have developed epiphora secondary to obstruction of a previously normal nasolacrimal duct in the presence of normal puncta and canaliculi; he was offered treatment by dacryocystorhinostomy but declined. Since ductal patency was not routinely evaluated, other injuries may have escaped detection. In one patient whose nasolacrimal duct was obstructed by tumor before treatment, a small plastic tube was passed through the inferior canaliculus, through the entire nasolacrimal drainage system, and out the nose; the tube was left in place for the entire treatment, and was maintained until 1 month after treatment. Permanent obstruction was not prevented.

Stenosis of the lacrimal puncta or canaliculi after high-dose irradiation was more common. Efforts to correct obstruction in the postirradiation period by conjunctivodacryocystorhinostomy were unsuccessful in two patients.

The Eyelids

Ectropion or entropion is seldom seen. Loss of the eyelashes is not a significant cosmetic problem. On occasion, however, some of the eyelashes that regrow turn inward (trichiasis) and must be surgically removed.

Figure 13-11. (*A*) Fifteen-year-old girl with an extensive orbital lymphoma. There were enlarged right preauricular and right jugulodigastric nodes. The right eye and entire lacrimal apparatus received 4000 cGy in 24 fractions over 34 days with cobalt-60. (*B*) There was no evidence of disease at 12 years. A cataract was extracted at 4 years. The patient tolerates a hard contact lens over the right eye (visual acuity 20/30) and has spectacle correction over the left eye (visual acuity 20/20). (*C*) The right fundus appears normal. Photograph was made at 8 years. (Parsons JT, Fitzgerald CR, Hood CI, Ellingwood KE, Bova FJ, Million RR. The effects of irradiation on the eye and optic nerve. Int J Radiat Oncol Biol Phys 1983;9:621, copyright © 1983, Pergamon Press)

Conjunctiva

Conjunctival telangiectasia is common after high-dose irradiation. It produces no symptoms.

Symblepharon is a rare, severe radiation injury in which the palpebral and bulbar conjunctiva are denuded of their epithelium and become adherent to one another.[20]

Sclera

Perforation of the sclera is rare, even with extremely high local doses used in treating malignant melanomas of the choroid and ciliary body.[20]

The Retina

When the lacrimal apparatus is shielded from high-dose irradiation, permanent visual loss secondary to degeneration of the anterior segment of the eye usually is preventable; a risk of radiation injury to the retina still exists, however. The retina is unique in that its small blood vessels are readily accessible to examination by ophthalmoscopy. Study of the retinal vasculature is aided by fluorescein angiography (Fig. 13-12). By using appropriate filters, it is possible to photograph the retinal vessels, including the capillary system, which cannot be visualized with an ophthalmoscope. The retina has one of the highest oxygen-consumption rates in the body and is supplied by an end-arterial system; that is, the arteries have practically no anastomoses with each other except at the capillary level. After arteriolar occlusion, the amount of collateral flow that can occur through capillary anastomoses is insufficient to prevent retinal damage.[3] Branches of the central retinal artery supply the inner retina, whereas the outer retina is supplied by the choroidal circulation by way of the posterior ciliary ar-

Figure 13-12. Normal fluorescein angiogram of left eye. The macula is situated about two disc diameters temporal to the optic disc. No capillaries are present within the foveal avascular zone. The remainder of the retina and optic disc show no nonperfused areas. Although the optic disc appears large when viewed with the ophthalmoscope, in the adult its average size is only about 1.5 mm. (Parsons JT, Bova FJ, Fitzgerald CR, Hood I, Mendenhall WM, Million RR. Tolerance of the visual apparatus to conventional therapeutic irradiation. In: Gutin PH, Leibel SA, Sheline GE, eds: Radiation injury to the nervous system. New York, Raven Press, 1991:292)

teries; irradiation may affect the vessels of both systems.[60]

MANIFESTATIONS OF RADIATION RETINOPATHY. Radiation retinopathy presents a clinical picture similar to that seen in diabetic retinopathy; it is likely that patients with diabetic small-vessel occlusive disease are at increased risk of radiation injury. Retinal injury after high-dose irradiation usually is not expressed clinically for 1½ to 3 years after irradiation, during which time visual acuity often remains normal. Subsequent deterioration is thought to occur because of progressive obliteration of small retinal vessels, resulting in retinal ischemia, edema, microaneurysm formation, capillary dilatation, hemorrhage, and retinal or nerve head neovascularization (Fig. 13-13). Retinal hemorrhages in the nerve fiber layer appear flame shaped, whereas deep retinal hemorrhages are round. Microaneurysms are most readily seen on fluorescein angiograms and usually are located near areas of capillary nonperfusion; although the precise pathogenesis of the microaneurysms is unclear, they are generally associated with vascular occlusive disease and retinal ischemia.

Retinal ischemia also is the likely cause of neovascularization. It is theorized that the hypoxic retina elaborates a vasoproliferative factor similar to that thought responsible for new-vessel formation in diabetic retinopathy. New vessels are situated on the retina, the optic disc, or both. As neovascularization progresses, the vessels invade the plane between the vitreous and retina, and eventually the vitreous itself. Patients with proliferative retinopathy have an unfortunate tendency to develop contracture of the vitreous gel; as the vitreous shrinks, neovascular fronds that have become attached to its posterior surface are pulled forward. Because the new vessels are fragile, preretinal or intravitreal hemorrhage results.[23] The vitreous also can exert traction on the retina, leading to retinal detachment.

Macular edema occurs due to incompetent perifoveal capillaries[23] and results in reduced central vision. Fluorescein angiography demonstrates leakage of dye.

Fluorescein angiography often delineates focal retinal capillary nonperfusion or occluded branch arterioles; central retinal artery occlusion has been described,[11,87,189] but has not been observed, in patients at the University of Florida. It seems that the capillaries are most susceptible to obliteration, followed by the smaller branch arterioles, whereas the main arterioles are least susceptible. Histologically, affected vessels have thick and hyalinized walls and the lumen may be occluded by a fine fibrillary material[23,60]; there may be total obliteration of small vessels. Leakage of plasma from damaged vessels, microaneurysms, or areas of neovascularization can be seen by fluorescein study.[87,160] Fluorescein angiography helps differentiate microaneurysms from small blot or dot hemorrhages.

Some patients with radiation retinopathy develop a neovascular proliferation on the anterior surface of the iris, called rubeosis iridis. The cause of anterior-segment neovascularization may be the same as for posterior-segment neovascularization (ie, a vasoproliferative factor produced by the hypoxic retina). Whether direct irradiation of the iris plays any role in producing rubeosis iridis is unknown. New blood vessels usually appear first at the pupillary margin, then progress to the angles, resulting in peripheral anterior synechiae and neovascular glaucoma, which is secondary to angle closure (Fig. 13-14). The vessels also are prone to hemorrhage, leading to hyphema. Rubeosis was preceded by ischemic optic neuropathy and central retinal vein occlusion in one patient.[160]

"Cotton-wool" exudates frequently are seen on ophthalmoscopic examination and are a direct result of retinal ischemia. Such lesions are not true exudates, but instead are microinfarcts in the nerve fiber layer. They usually appear round and are seldom wider than the optic disc. True retinal exudates (also called *hard* or *waxy* exudates) also may be seen, and are presumably due to extravasation of fluid from abnormally permeable vessels. They are most common near microaneurysms and have a particular predilection for the region of the macula. With time, the fluid is resorbed, leaving behind a protein- or lipid-rich residue.[102] Most commonly, there is a 2- to 3-year period during which the visual acuity remains normal or near normal; then, over several months, the vision progressively deteriorates. If the dose to the retina was only 5000 to 5500 cGy, there may be a longer latent period (eg, 5 to 6 years). If the dose was lower still, retinal changes that may be noted on ophthalmoscopic examination (including microaneurysms, cotton-wool patches, telangiectasis, and so on) may produce no alteration of visual acuity and may remain stable with prolonged follow-up (10 to 22 years).[9]

Visual loss usually is painless unless neovascular glaucoma develops, as it did in 10 patients at the University of Florida. Pain from the latter condition could not be controlled by medical means, by retrobulbar injections of alcohol, or by cyclocryotherapy (cryotherapy ap-

(text continues on page 268)

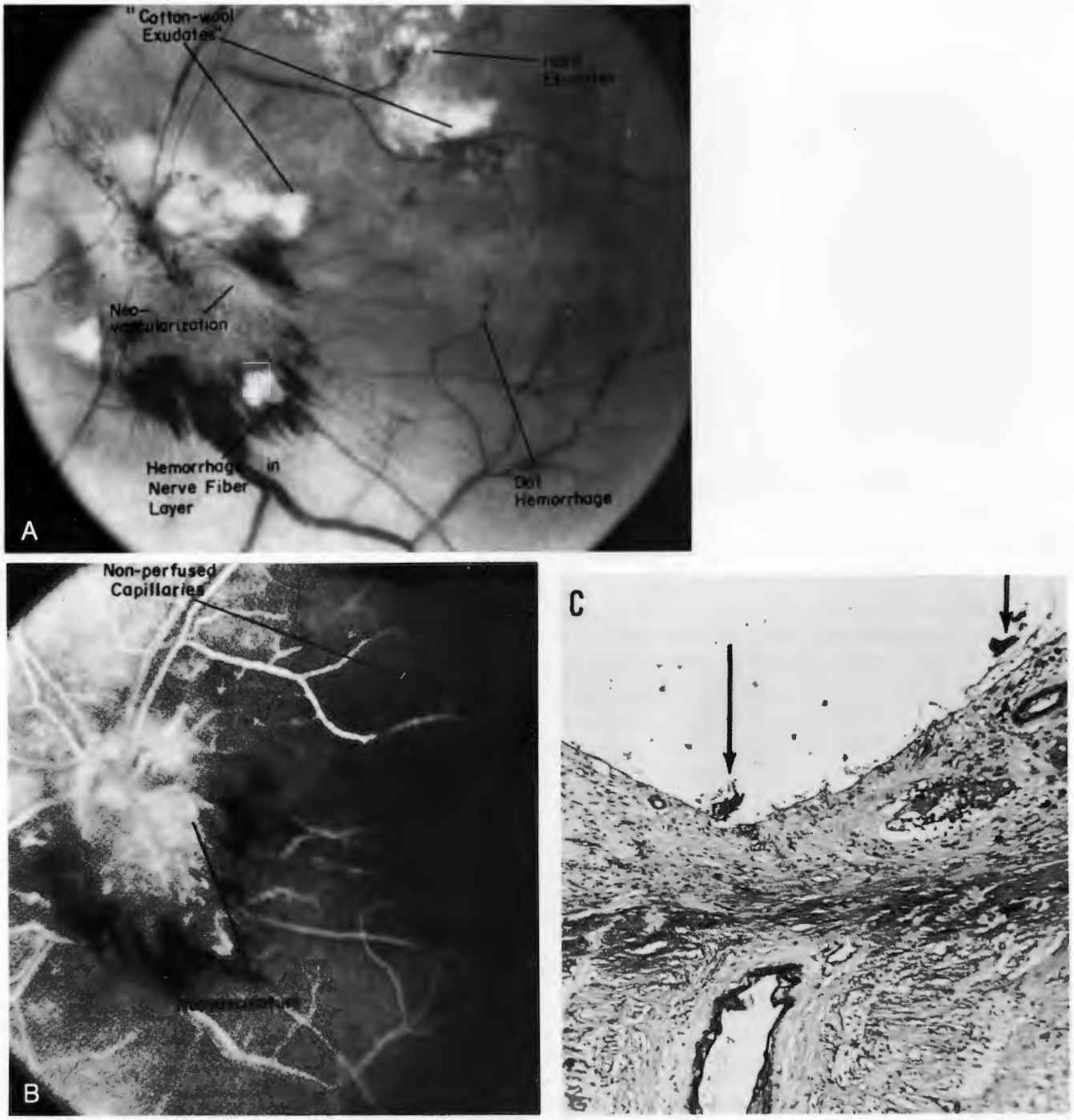
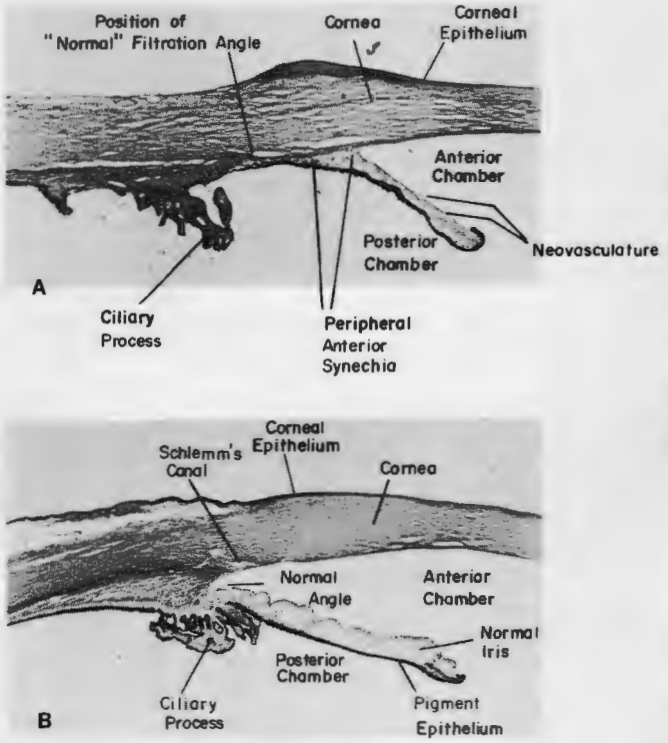
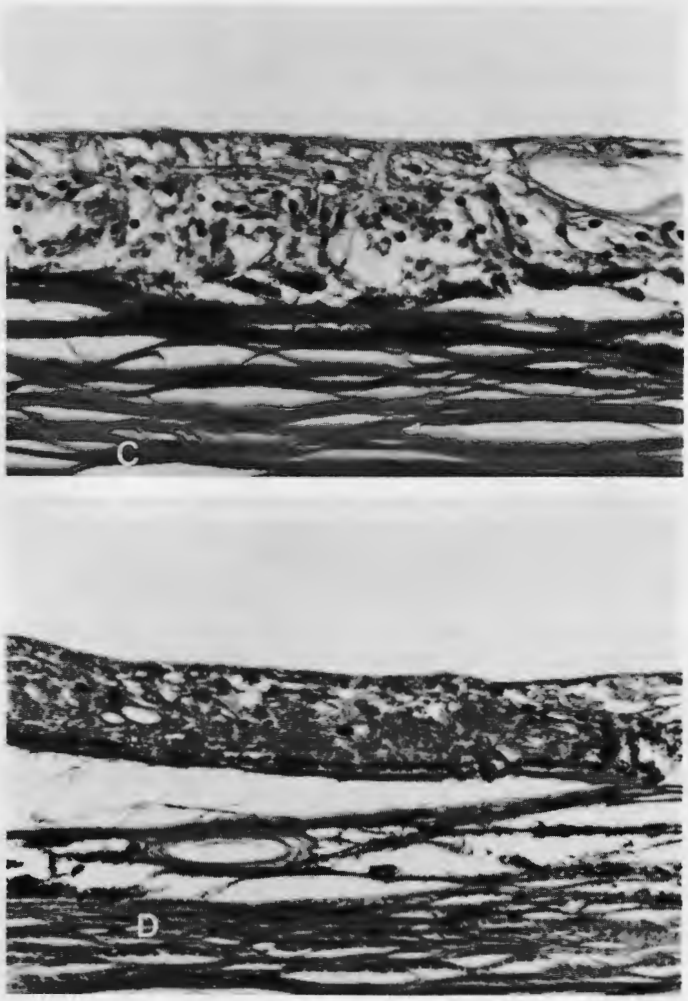


Figure 13-13. (*A*) Appearance of left eye on ophthalmoscopic examination 2 years 8 months after irradiation of a low-grade fibrosarcoma of the left nasal cavity, paranasal sinuses, and orbit in a 42-year-old woman. The dose to the left retina was 6000 cGy in 32 fractions over 61 days by split-course technique; the lacrimal gland was shielded. Visual acuity remained 20/20 in the left eye for 2 years after irradiation, but by 2 years 7 months she had developed an edematous, congested optic disc; her visual acuity was 20/300. One month later, at the time of this photograph, there was a Marcus-Gunn pupil, and vision was "counts fingers"; the disc margins were hazy and there were cotton-wool spots, hard exudates, intraretinal and preretinal hemorrhages, and irregular, tortuous branch retinal arterioles. (*B*) Fluorescein angiography showed irregular fluorescence of the large vessel walls superiorly, compatible with damage to these structures. There was an extensive fluorescein leak from neovascular tissue over the disc, and an area of retinal capillary nonperfusion superior to the fovea. Several months later, the patient presented to her local ophthalmologist with severe pain secondary to neovascular glaucoma (40 mmHg). Enucleation was performed. In addition to rubeosis iridis, the surgical specimen showed neovascular tissue arising from the surface of the nerve head and extending into the vitreous. (*C*) Photomicrograph of the eye after enucleation, showing cluster of small, thin-walled neovasculature protruding from the surface of the nerve head into the vitreous (*arrows*). The neovasculature corresponds to the area of leakage noted on fluorescein angiography. (*A* and *B* from Parsons JT, Fitzgerald CR, Hood CI, Ellingwood KE, Bova FJ, Million RR. The effects of irradiation on the eye and optic nerve. Int J Radiat Oncol Biol Phys 1983;9:614, copyright © 1983, Pergamon Press; *C* from Parsons JT, Bova FJ, Fitzgerald CR, Hood I, Mendenhall WM, Million RR. Tolerance of the visual apparatus to conventional therapeutic irradiation. In: Gutin PH, Leibel SA, Sheline GE, eds. Radiation injury to the nervous system. New York, Raven Press, 1991:293)





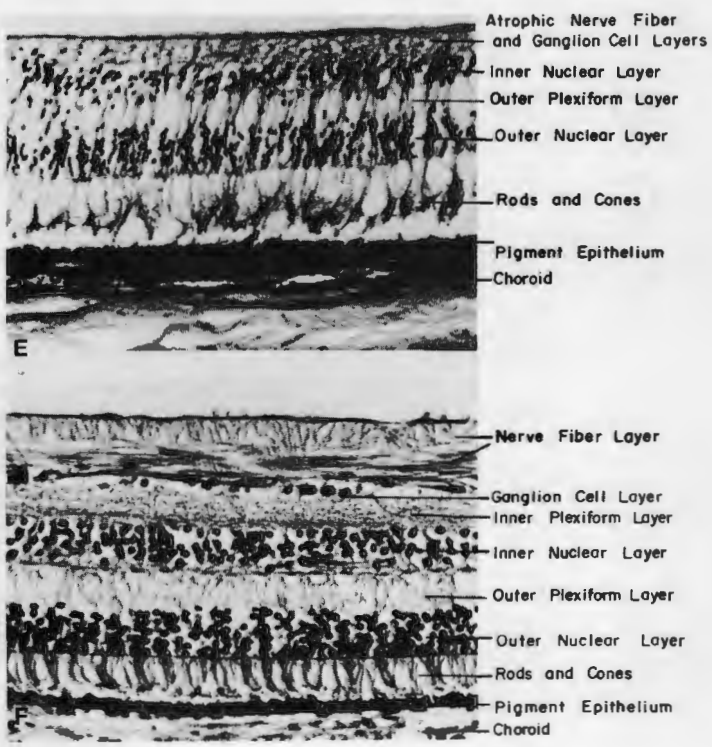


Figure 13-14. A 47-year-old man received 6500 cGy in 32 fractions over 44 days to the nasal half of his right eye for a poorly differentiated cancer involving the ethmoid sinus and orbit. The position of the eye during treatment was "lateral gaze." Until 14 months after treatment, he noted only epiphora, which had been present before treatment, and occasional flashes of light in the right eye; visual acuity remained 20/40. Three months later, there was severe sheathing of retinal arterioles and declining visual acuity. At 22 months, vision was "counts fingers" and the patient complained of ocular pain. Ocular tension was 44 mmHg. Pain was progressive and unrelieved by narcotic analgesics and carbonic anhydrase inhibitors. Blood in the anterior chamber (hyphema) was noted. Enucleation was required. (*A*) The surgical specimen showed rubeosis iridis (note numerous dilated vessels on the anterior surface of the iris), ectropion uveae, and a broad, peripheral anterior synechia, which obliterated the filtration angle. (*B*) Normal iris and normal filtration angle for comparison with *A*. (*C*) The retina was in place. Retinal charges were most severe in those portions of the retina that received the highest dose. Microscopic section shows severe atrophy and disorganization of the nasal (irradiated) retina. (*D*) Microscopic section from another area of the nasal retina showed full-thickness retinal necrosis. (*E*) The temporal retina, which received a low dose of irradiation, showed only the effects of elevated intraocular pressure, rather than effects due to a direct action of irradiation. The nerve fiber layer was atrophic and the ganglion cells absent. Nuclei of the inner nuclear layer were decreased in number, whereas those of the outer layer were preserved. (*F*) Appearance of normal retina for comparison with *C* through *E*. The histologic changes secondary to irradiation are nonspecific. (Parsons JT, Fitzgerald CR, Hood CI, Ellingwood KE, Bova FJ, Million RR. The effects of irradiation on the eye and optic nerve. Int J Radiat Oncol Biol Phys 1983;9:609–622, copyright © 1983, Pergamon Press)

plied to the ciliary body to decrease aqueous production); enucleation or evisceration of the glaucomatous eye was necessary for pain relief in eight patients, and was recommended but not undertaken in another.

TIME–DOSE ANALYSIS FOR RETINAL INJURY. A log–log plot of dose versus number of fractions for retinal injury sufficient to produce visual loss after irradiation of the retina is shown in Figure 13-15. The major lacrimal gland in these patients was shielded throughout treatment (21 eyes), most commonly with field arrangements as shown in Figure 13-5*B* and *C*, or it was shielded after it had received less than or equal to 4500 cGy (7 eyes); patients who lost sight secondary to anterior-segment degeneration are excluded. Patients in whom the central retina was shielded by a cylindrical lead corneal block on the anterior field, while gazing straight ahead, also were excluded, since determination of the retinal dose is not possible in this situation.[160]

The shape of the sigmoid dose–response curve is steep between 5000 and 6000 cGy. There was only one instance of clinically detectable retinal injury at or below 5000 cGy (a 10-year-old patient who had a vitreous hemorrhage 13 months after 4500 cGy plus cyclophosphamide). Above 5000 cGy, only one retina was not severely injured and this case was equivocal. The retina of this patient received 6000 cGy in 35 fractions; vision was lost at 2½ years secondary to a dense cataract. Because of moderate dry-eye symptoms in a nonseeing eye, enucleation was undertaken at 4 years, 2 months. Although retinal function could not be assessed, the retina and retinal vessels were normal on histologic examination. Analysis of risk of injury versus time–dose factors is difficult because few data on risks of dosages between 5000 and 5500 cGy exist. Of the four patients whose eyes received these doses, one also received multiagent chemotherapy (the interaction between irradiation and chemotherapy almost certainly increases the risk of injury[23,29,79]), and two were treated with large-dose fractions (305 to 325 cGy per fraction). The best estimate from available data is that a significant risk exists of severe injury when retinal doses exceed 5000 cGy (at 180 to 200 cGy per fraction). Bessell and associates noted no retinal vascular abnormalities in 10 patients who were investigated by fluorescein angiography after retinal doses of 2500 to 3000 cGy for lymphomas (minimum follow-up, 1 year).[13]

MANAGEMENT OF RADIATION RETINOPATHY. Even in the presence of severe retinopathy that results in blindness, maintenance of the eyeball is preferable to enucleation or evisceration unless the eye is painful. If the eyeball is removed, cosmesis is difficult to restore in

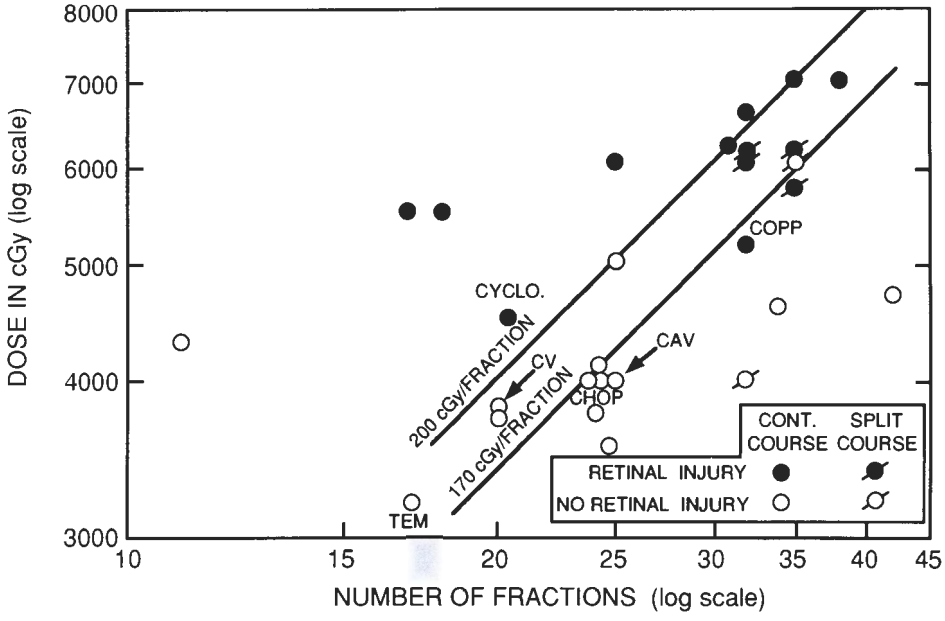


Figure 13-15. Retinal dose versus number of fractions for production of radiation retinopathy. Included are data on 28 eyes (27 patients) after continuous- or split-course irradiation (cobalt-60 or 2 MV) of a variety of head and neck tumors at the University of Florida (October 1964 through March 1979). All patients have been observed for a minimum of 3 years and the maximum follow-up is 16 years; patients who died within 3 years without developing retinal injury are not included. Reference lines for treatments administered at 170 cGy per fraction and 200 cGy per fraction have been added for ease of interpretation of the data; these lines are not isoeffect lines. There is a mean follow-up of 6.6 years and a median follow-up of 5.5 years in the 15 uninjured eyes. Severe injury was documented in the remaining 13 eyes at 1 to 6.5 years after treatment; mean and median times to injury were both 2.5 years. Ten of the 13 injuries were detected within 3 years. Six patients (seven eyes) who received single-agent or multiagent chemotherapy in addition to irradiation are so designated. Visual acuity in the injured eyes was 20/200 in one eye, "counts fingers" at 1 or 2 feet in two eyes, "hand motion" in one eye, "light perception" in three eyes, and "no light perception" in six eyes. (Parsons JT, Fitzgerald CR, Hood CI, Ellingwood KE, Bova FJ, Million RR. The effects of irradiation on the eye and optic nerve. Int J Radiat Oncol Biol Phys 1983;9:617, copyright © 1983, Pergamon Press)

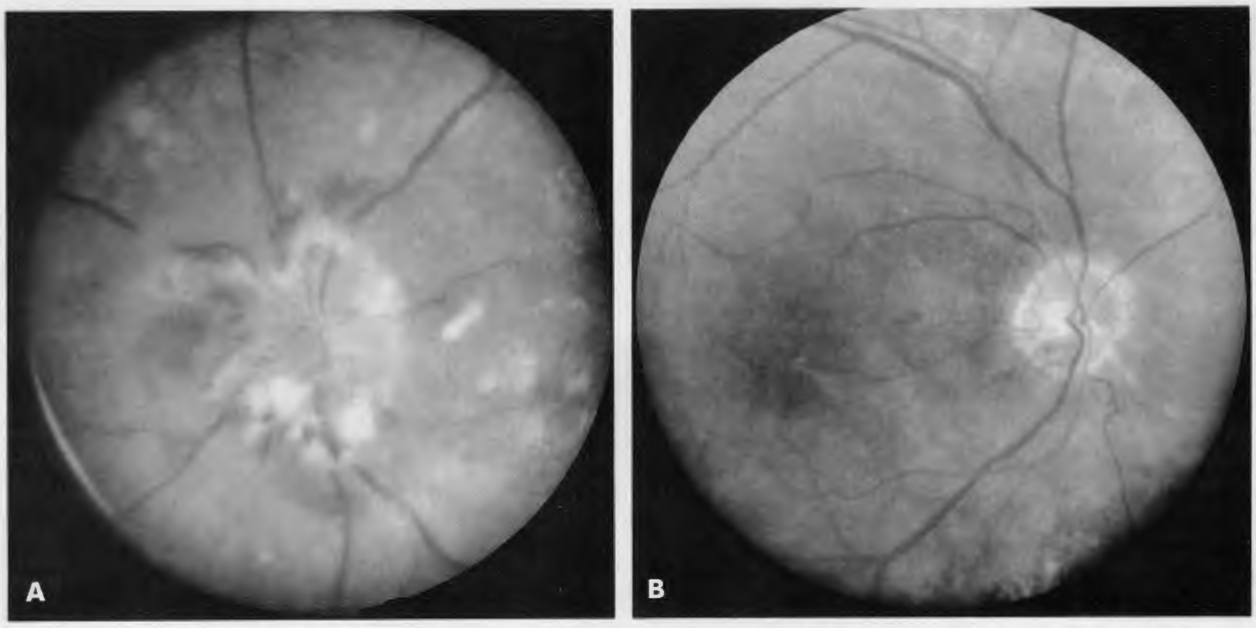


Figure 13-16. (*A*) Right eye of 66-year-old man 16 months after 4000 cGy to the posterior half of the right retina. Because of inhomogeneity in the dose distribution, the posterior pole of the eye received 5000 cGy to 5500 cGy in the area of the nerve head. Visual acuity was 20/100. There is extensive disc edema with surrounding hemorrhages and exudates. On fluorescein angiography, there were tremendously dilated capillaries on the optic disc with an extensive late leak with some areas of retinal nonperfusion. The patient underwent panretinal laser photocoagulation. By 4 months, the capillary dilation at the nerve head had diminished markedly. In the ensuing months, the hemorrhages and exudates gradually resolved. (*B*) At the time of this photograph (1 year after laser photocoagulation), the disc edema had dissipated. Visual acuity was 20/25. (From Parsons JT, Bova FJ, Fitzgerald CR, Hood I, Mendenhall WM, Million RR. Tolerance of the visual apparatus to conventional therapeutic irradiation. In: Gutin PH, Leibel SA, Sheline GE, eds. Radiation injury to the nervous system. New York, Raven Press, 1991:298)

heavily irradiated patients. Orbital implants (to take up dead space) frequently are extruded because of progressive fibrosis and contraction of the orbital soft tissues. Ocular prostheses are likewise unsatisfactory after high-dose irradiation, and most patients prefer to wear a patch. Since the only effective treatment of neovascular (closed angle) glaucoma is removal of the eyeball, efforts should be made to prevent this complication. In diabetic patients with proliferative retinopathy, panretinal laser photocoagulation eliminates the stimulus to new vessel formation in the anterior and posterior segments, reducing the risk of developing glaucoma.[208] The rationale is to destroy hypoxic areas of the retina that are believed to produce a vasoproliferative factor. Laser photocoagulation at the University of Florida on a small number of patients suggests that this therapy may be beneficial (Fig. 13-16). Chee and Gass reported some success with photocoagulation when treating macular exudates due to radiation retinopathy.[30,73] Thompson and coworkers treated one patient with argon laser panphotocoagulation for proliferative retinal neovascular changes and vitreous hemorrhage; the new vessels regressed, and there was no recurrence of hemorrhage.[202] Kinyoun and coworkers reported that focal photocoagulation of microaneurysms and other sites of leakage identified on fluorescein angiogram was effective in preventing further loss of vision from macular edema in five of five treated eyes.[100] The same authors treated six eyes with panretinal photocoagulation for new vessels on the disc and retina; they noted regression of neovascularization in three eyes, whereas in the other three eyes, dense vitreous hemorrhages subsequently occurred, requiring vitrectomy for restoration of useful vision. They concluded that because of the clinical and histologic similarities between radiation retinopathy and diabetic retinopathy, it is reasonable to base treatment of radiation retinopathy on established guidelines for treating diabetic retinopathy.

PREVENTION OF RADIATION RETINOPATHY. All fields should be treated daily. Contours and isodose plans through the level of the eyes should be obtained. The dose per fraction should not exceed 180 to 190 cGy/d to the retina. If feasible, fields should be reduced to limit the retinal dose to 5000 cGy or less. In the last several years, physicians at the University of Florida have used hyperfractionation to reduce the risk of complications.

When only a portion of the eye is irradiated, its position during treatment is important. Until 1970, patients at the University of Florida with ethmoid sinus carcinomas were instructed to gaze laterally to displace the ipsilateral crystalline lens from the treatment field (see Fig. 13-5*B*); the field edge was at or near the medial limbus. This position rotated the posterior pole, and thus most of the sensory retina, into the treatment field. Currently, patients are instructed to gaze straight ahead with the lids open to prevent bolus effect.

Ten patients who had no evidence of orbital invasion

were treated using an anterior field that transsected the eyeball at the medial limbus, with straight-ahead gaze (see Fig. 13-5*D*). These patients have had follow-up for 3.5 to 10 years (mean, 5.5 years; median, 6 years). It is impossible to gauge the dose to the medial one third of the eye, since it lies in the penumbra of the anterior portal. No detectable retinopathy has occurred, but three eyes lost sight due to retrobulbar optic nerve injury.

On the anterior portal, many centers use a so-called corneal cylinder on a blocking tray that is located 15 to 20 cm from patients. At the University of Florida, it is preferred to use no cylinder and, instead, to reduce the portals whenever possible after a dose that is believed to be safe. Using a long cylinder that allows little transmission of x-rays has the undesirable effect of shielding areas potentially involved by tumor. If a short cylinder is used (eg, 1 HVL or less), then the dose to the retina might be limited to 5000 cGy for a 7000-cGy treatment course. The two techniques that limit retinal dose (ie, portal reduction and a short corneal cylinder) produce a different effect on the retina; although the total retinal doses for the two techniques might be nearly the same, the former delivers 5000 cGy in 27 to 28 fractions over 5½ weeks before fields are reduced, whereas the dose from the latter technique would be spread out over the entire treatment (eg, 5000 cGy in 38 fractions over 7½ weeks). The latter technique, which has not been tried, would spare not only the eye, but also cancer in the orbit.

The Optic Nerve

OPTIC ATROPHY. Optic atrophy is the end result of conditions that produce degeneration of axons anterior to the lateral geniculate body. It is a descriptive term that does not imply a specific etiology or mechanism of injury. Diagnosis is based on the ophthalmoscopic appearance of a pale optic disc with defective visual function. A loss of visual acuity, visual field defects, or both may occur. If the lesion producing the atrophy is in the retina, then ascending optic atrophy occurs; if the defect is in the optic nerve fibers, descending optic atrophy takes place. A reduction in the vascularity of the optic nerve head occurs, so that on ophthalmoscopic study the disc is pale or white, rather than its normal pink color. Fluorescein angiography reveals a loss of vessels in both the superficial and deep vascular networks.

OPTIC NEUROPATHY. Two types of optic neuropathy (anterior ischemic optic neuropathy and retrobulbar ischemic optic neuropathy) may be seen after irradiation. Both types are believed to be caused by vascular occlusive disease, with an interruption of blood supply to either the nerve head or the retrobulbar portion of the nerve, respectively. Patients with preexisting small-vessel occlusive disease are at increased risk.

Ophthalmoscopic findings in *anterior ischemic optic neuropathy* are those of disc pallor and edema with splinter hemorrhages on or adjacent to the disc; the clinical picture is similar to that seen in patients with papilledema. Although it might be possible for only one sector of the disc to be involved, this was not observed in the University of Florida series. Five eyes in four patients developed such injury; there was a 2-year latency period in three eyes, a 3-year latency period in one eye, and a 4-year latency period in the fifth eye. Treating three patients (four optic nerves) with orally administered corticosteroids failed to halt progressive loss of vision over a period of several months. Visual acuity in two eyes became 20/400; the other three had no light perception. Disc pallor eventually resulted and was permanent. Brown and coworkers reported on six patients who developed a clinical picture of ischemic optic neuropathy at an average of 19 months after treatment with 3600 to 7000 cGy of external-beam irradiation to the area of the anterior optic nerve.[22] In their series, the acute picture of nerve-head swelling and peripapillary hemorrhages and exudates persisted for several months, followed in most instances by optic atrophy. However, in two patients, visual acuity improved from 20/200 at the onset of acute disc swelling to 20/30 and 20/40 over 10 weeks to 6 months, respectively; one of the patients received oral glucocorticosteroids and the other HBO therapy, but the authors were unconvinced that these therapies were responsible for the observed recovery.

Seven eyes in five patients from the University of Florida developed visual loss secondary to *retrobulbar ischemic optic neuropathy*, that is, proximal injury to the nerve without evidence of disc edema or hemorrhage. Time to onset of injury in patients from the University of Florida was sometimes shorter than in the series from M.D. Anderson Hospital (Houston), in which Shukovsky and Fletcher noted a 4- to 5-year latency interval.[189] Visual difficulties first were noted at 11, 12, 14, 28, 42, 72, and 100 months, and were thought by the patients to have occurred suddenly in all seven instances.

Three eyes initially lost vision in all fields at the onset of injury. In the other four eyes, the initial visual symptom was a field defect. In both our series and other reported cases, the defects noted most frequently have been altitudinal, similar to the defects most commonly observed in patients with vascular occlusive disease affecting the optic nerves.[19,44,180] Within 2 weeks to 2 months after they lost a portion of the visual field, the remaining field of vision also abruptly became affected in three of the four eyes; the fourth patient died 10 months after developing an altitudinal defect and had no progression of the deficit during the final 10 months of follow-up. Ophthalmoscopic examination shortly after the onset of symptoms usually revealed a normal-appearing disc or a disc with pallor of only one sector. There was eventual progression to a chalk-white disc in these patients (Fig. 13-17). Visual acuity became "count fingers at 1 or 2 feet" in two eyes, "light perception" in the third, and "no light perception" in the other four eyes.

TIME–DOSE ANALYSIS FOR OPTIC NERVE INJURY. The risk of injury correlates best with daily fraction size for patients who received greater than 5500 cGy (Fig. 13-18). At approximately 165 to 190 cGy per fraction, a dose of 6000 to 7300 cGy produced injuries in 8% of long-term survivors (2 of 24). After daily doses of 195 cGy or greater, the risk within the same dose range was substantially greater (41%, or 7 of 17).[160] Some series have reported optic nerve injuries after doses as low as 5000 cGy, generally in patients with pituitary adenomas, who commonly present with optic nerve deficits secondary to mass effect. Previous compromise of the nerve increases the risk of injury; patients with pituitary adenoma were excluded from the University of Florida series.

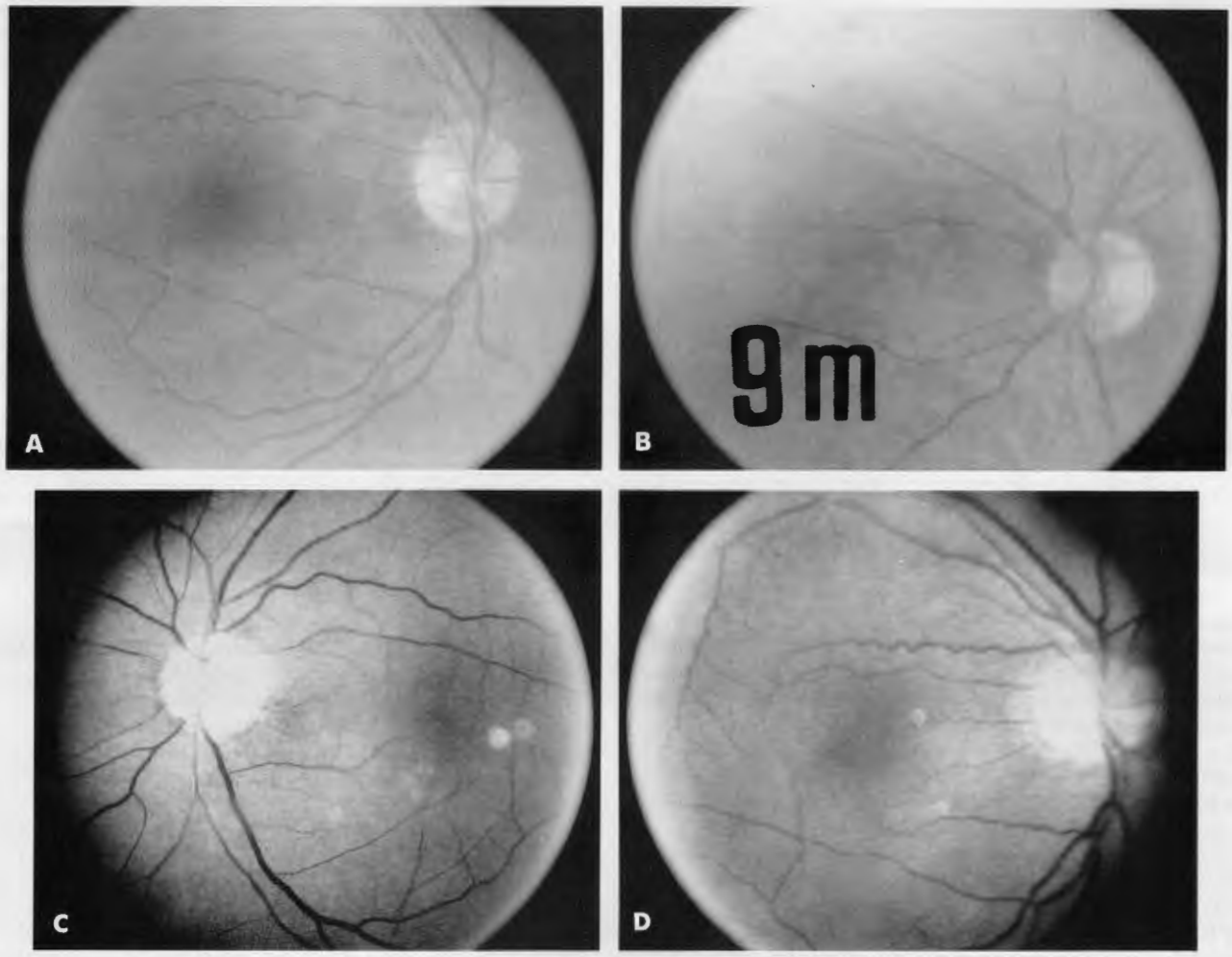


Figure 13-17. Right (*A*) and left (*B*) fundi 9 months after treatment of squamous cell carcinoma of the nasal cavity and ethmoid sinuses in a 70-year-old man who received 6000 cGy in 30 fractions over 43 days followed by a radium needle implant for 2000 cGy. The left optic nerve received approximately 6200 cGy and the right optic nerve approximately 5900 cGy. Both fundi appeared normal. (*C*) At 11 months after treatment, there was optic atrophy of the left eye (visual acuity "hand motion"). Fluorescein angiography revealed a paucity of disc capillaries in both eyes. (*D*) At 14 months, the patient noted a visual field defect in the right eye. At this time there was an area of pallor on the temporal side of the disc. Visual acuity remained 20/20 in the right eye, but over the next 2 weeks, visual acuity became "no light perception" in both eyes. (Parsons JT, Bova FJ, Fitzgerald CR, Hood I, Mendenhall WM, Million RR. Tolerance of the visual apparatus to conventional therapeutic irradiation. In: Gutin PH, Leibel SA, Sheline GE, eds. Radiation injury to the nervous system. New York, Raven Press, 1991:300)

MANAGEMENT OF OPTIC NERVE INJURY. Although a preliminary report on the use of HBO therapy for radiation-induced optic neuropathy was encouraging,[81] HBO had no demonstrable efficacy in a larger series. Roden and coworkers treated 13 patients who had delayed radiation injury to the optic nerves or chiasm after 4500 to 7200 cGy.[174] Patients received HBO therapy consisting of repeated treatments with 100% oxygen at 2 atm for 2 hours; 11 patients received corticosteroids simultaneously. Treatment was undertaken as soon after diagnosis as possible; in 6 of 13 patients, therapy was begun within 1 month of recognized visual loss. No patient's vision improved during treatment or follow-up, which lasted between 1 and 4 years. In fact, many patients had continued deterioration of visual acuity after HBO therapy. Patients whose treatment was initiated early after recognized visual loss had no better outcome than those treated later.

No effective therapy currently exists. Efforts should be directed at prevention by portal reductions, where possible, hyperfractionation, and lower-dose irradiation combined with surgery rather than high-dose irradiation alone.

The Lens

Under the anterior lens capsule, a layer of epithelial cells exists. Under the posterior capsule, there is no epithelium. Toward the equator, the epithelial cells become progressively elongated and are transformed into lens fibers; the fibers are 7 to 10 mm in length and contain a flattened nucleus, located near the equator. Subcapsular

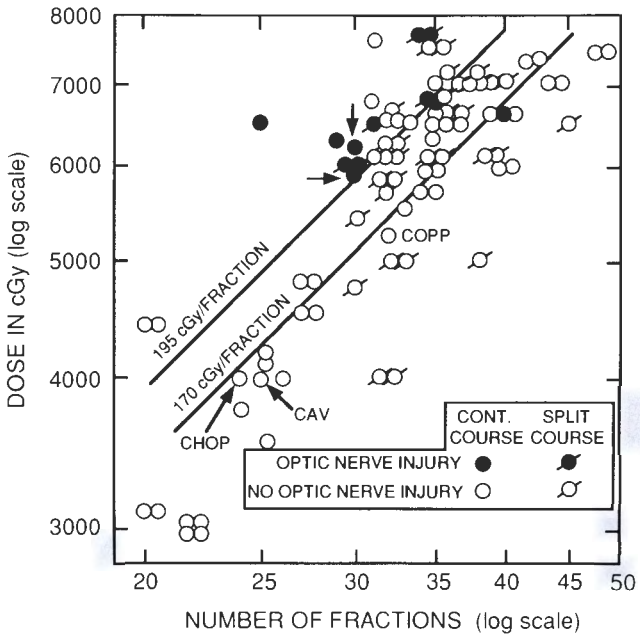


Figure 13-18. Dose versus number of fractions for optic nerve injury secondary to irradiation. Included are data on 92 optic nerves in 55 patients after continuous or split-course irradiation (cobalt-60 or 2 MV) of a variety of head and neck tumors at the University of Florida (October 1964 through March 1979). All patients had 3 to 14 years of follow-up; patients who died within 3 years without developing optic nerve injury are excluded. Eyes that lost sight due to severe retinal injury are also excluded. The mean follow-up was 6.35 years, and median 6.5 years, for the 80 optic nerves that showed no clinical evidence of injury after irradiation. Eight of 12 injuries were detected by 3 years. Reference lines for treatments administered at 170 cGy per fraction and 195 cGy per fraction have been added for convenience of interpreting the data; these lines are not isoeffect lines. Two optic nerves (*arrows*) received an additional small dose from a radium implant (approximately 200 cGy to the optic nerves) after external irradiation. Three patients who received concomitant chemotherapy are so designated. (Parsons JT, Fitzgerald CR, Hood CI, Ellingwood KE, Bova FJ, Million RR. The effects of irradiation on the eye and optic nerve. Int J Radiat Oncol Biol Phys 1983;9:619)

epithelial cells are capable of reproduction; most of the dividing cells are located in the anterior equatorial region. These dividing preequatorial cells are thought to be susceptible to the effects of ionizing radiation. Since the number of mitotic cells decreases with age, the lenses of adults are less susceptible to radiation than those of infants and children.

Strictly interpreted, any opacity in the normal transparent crystalline lens constitutes a cataract. The earliest changes are detectable only on slit-lamp examination, when patients are still asymptomatic. As a cataract progresses, it causes visual disturbances, including glare, image blur, and eventually blindness. If vision in the opposite eye is normal, some patients are not aware of a unilateral cataract, even when vision in the affected eye is severely impaired.

RADIATION CATARACTS. The morphology of radiation cataracts has been well described.[136] The initial change is vacuole formation in the equatorial region, secondary to injury to the dividing epithelial cells.[116] These opacities (composed of degenerate fibers and cell debris) slowly migrate posteriorly to the posterior subcapsular zone. Ophthalmoscopically, the opacity initially appears as a dot at the posterior pole of the lens, then gradually enlarges to 1 to 2 mm. Scattered granules and vacuoles are seen around the central opacity. With further enlargement, the opacity develops a clear center so that it assumes a doughnut shape. At about the same time, granular opacities appear in the anterior subcapsular zone. Depending on the radiation dose and its fractionation, the cataract may remain stationary at any stage of development and produce little or no visual impairment; conversely, it may become a nonspecific, mature cataract, indistinguishable from other types of cataract, resulting in complete blindness.

The time to onset of clinically detectable lenticular opacities is inversely related to dose. Fractionation lengthens the latency period. After low-dose irradiation, the latent period may be many years, whereas very intense exposures result in a progressive cataract within 6 months. Several patients from the University of Florida did not develop cataracts until 3 to 3½ years after 4000 to 7000 cGy to the lens with external-beam irradiation.

TIME–DOSE ANALYSIS FOR CATARACT FORMATION. The largest body of clinical data relating cataract formation to dose comes from Merriam and Focht.[136] In 1957, they published data on 173 patients from the Memorial Center and the Radiotherapy Department of the Institute of Ophthalmology, Columbia Presbyterian Medical Center, New York City. Patients were treated for a wide variety of benign and malignant conditions using different techniques, including low-dose-rate continuous irradiation from gold seeds or radium plaques; orthovoltage external-beam irradiation alone was used in only 16 adult patients. Treatments were reconstructed as accurately as possible on a phantom skull, and dose measurements were made at the lens with a small ionization chamber. Regardless of the degree of fractionation, all patients who received at least 1150 R to the lens developed some degree of cataract; above 1450 R, all cataracts were progressive. The work of Merriam and Focht[136] agrees with that of Cogan and Dreisler,[33] who noted radiation cataracts in three of five adult patients whose lenses had received 600 to 1000 R fractionated external-beam orthovoltage irradiation for orbital or conjunctival lymphomas; the two cataract-free patients had had follow-up for only 2½ and 3 years, respectively, and so still were at risk. Other investigators suggest that somewhat higher doses may be given without producing clinically significant cataracts.[21,155] Data from the University of Florida do not lend themselves to a time–dose analysis of radiation cataractogenesis, since all patients who received high doses developed cataracts, whereas those who received low doses had their lenses protected by eye shields or corneal cylinders, making dose determination impossible.

Deeg and associates examined 277 patients who had follow-up for 1 to 12 years after bone marrow transplantation.[46] Ninety-six patients received a conditioning regimen of chemotherapy alone, whereas 181 received both chemotherapy and total body irradiation (TBI). TBI was administered as either a single dose of 1000 cGy (105 patients), or in six or seven 200- to 225-cGy fractions (one fraction per day) to a total dose of 1200 to 1575 cGy (76 patients). Figure 13-19 shows the probability of requir-

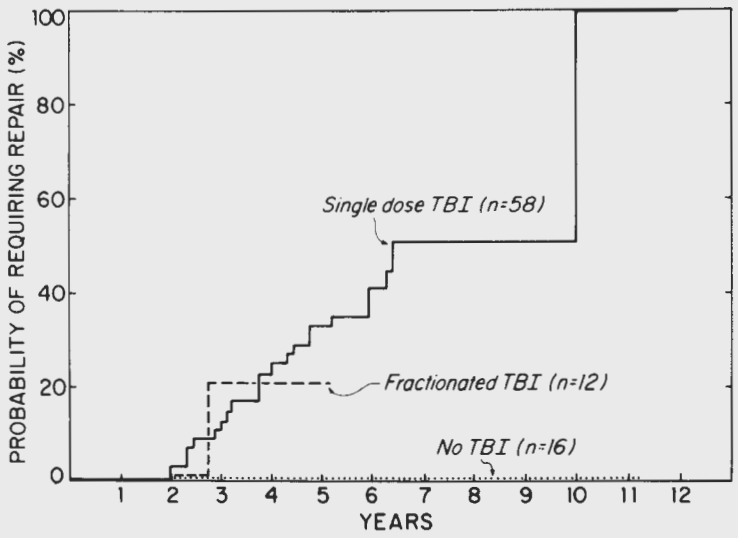


Figure 13-19. Kaplan-Meier product limit estimates of the probability of requiring surgical repair of cataracts after marrow transplantation among patients given single-dose, fractionated, or no total-body irradiation. (Deeg HJ, Flournoy N, Sullivan KM, Sheehan K, Buckner D, Sanders JE, Storb R, Witherspoon RP, Thomas ED. Cataracts after total body irradiation and marrow transplantation: a sparing effect of dose fractionation. Int J Radiat Oncol Biol Phys 1984;10:960)

ing surgical repair of clinically significant cataracts after marrow transplantation according to the treatment regimen. Unirradiated patients did not develop cataracts that required repair. Patients who received fractionated TBI had a 21% 5-year probability of repair, whereas patients who received single-dose TBI had 34% 5-year and 100% 11-year probabilities. Further follow-up is necessary to determine whether a higher percentage of the fractionated group eventually develops significant cataracts.

Bessell and coworkers reported life-table estimates of the probability of developing a cataract after fractionated irradiation of orbital lymphomas.[13] For patients who received 1500 cGy to the germinative zone of the lens, 5- and 8-year probabilities of cataract formation were 12% and 28%, respectively. The 5-year probability for patients who received 3000 cGy was 64%; the authors concluded that it is likely that all of these patients eventually will develop cataracts.

MANAGEMENT OF RADIATION CATARACTS. Some radiation cataracts produce few or no symptoms and require no treatment. Even if a cataract impairs vision, it may not require removal if patients have good vision in the other eye. If cataract extraction is performed, visual rehabilitation may be more difficult than in unirradiated patients. It is not possible to use spectacles with an aphakic lens over only one eye, since the thick aphakic lens produces a 30% to 35% magnification of objects in the field of view, with resultant image size discrepancy and diplopia. Although a contact lens largely avoids the problems of image magnification and image size diplopia, it is not likely to be well tolerated if the eye is dry from prior irradiation (ie, if the dose to the whole eye and lacrimal apparatus was greater than 4000 cGy) (see Fig. 13-11). If patients are not able to wear a contact lens after extraction, they function better if the cataract is not removed (assuming that good vision exists in the contralateral eye). If cataract extraction becomes necessary because of severe glare or another problem, surgery can usually be accomplished without a greatly increased risk of operative complications. The physician should evaluate retinal function with bright-flash electroretinography and transscleral visual-evoked response before cataract extraction, since extraction produces little or no improvement if radiation retinopathy also is present. If the retinal dose was greater than 5500 cGy, extraction is probably pointless in terms of restoration of vision. In two recent patients, cataract extractions were performed about 2 years after retinal doses of approximately 7000 cGy; although the prospects of maintaining useful vision essentially are zero in these patients, extractions may allow the ophthalmologist to closely observe the retina and apply the laser, should neovascularization occur, thus preserving the eyeball.

The University of Florida has had limited experience (three patients) with intraocular lens implantation in heavily irradiated eyes; the procedure is not recommended, since the operation requires greater intraocular manipulation than routine extraction and carries an increased risk of complications. The implants were performed at 2, 2½, and 4 years after 5100 cGy, 3500 cGy, and 6000 cGy, respectively, to the entire eye; in all three patients, the major lacrimal gland had been shielded. The first patient required reoperation to replace a dislocated lens. Postoperatively, she developed uveitis and severe corneal edema, leading to aphakic bullous keratopathy with severe pain and irritation; a conjunctival flap was required to relieve pain from the keratopathy, and all useful vision was lost. Visual acuity in the second patient returned to 20/15, and there were no operative complications. The third patient never achieved better than 20/200 visual acuity in the operated eye and also had postoperative keratopathy.

Newer techniques (posterior chamber rather than anterior chamber implants) should be safer.

The Orbit

Ten patients from the University of Florida who received high-dose irradiation to the eye underwent evisceration or enucleation to relieve pain caused by neovascular glaucoma and/or corneal complications. In three patients, a glass or silicone orbital implant was sutured in place to take up the orbital dead space and improve cosmesis. In all three patients, the implants were spontaneously extruded 1 to 5 months postoperatively because of progressive fibrosis and contraction of the orbital soft tissues. Several patients were fitted with ocular pros-

theses but often were dissatisfied with them, since frequently they were irritating or would pop out when patients blinked or sneezed. Most patients prefer to wear a patch full time or wear the prosthesis for only a few hours each day.

The Ear

Serous Otitis Media

Serous otitis media is a frequent complication of irradiation of cancer of the paranasal sinuses and nasopharynx, occurring in at least 15% to 20% of patients. Patients with nasopharyngeal cancer often present with otitis because of tumor obstruction of the eustachian tube. When tubal patency is compromised, oxygen in the middle ear is absorbed by the blood vessels of the mucous membrane, resulting in a relative negative pressure; the tympanic membrane becomes retracted, and an effusion results. Patients whose tumors involve the eustachian tube are at greater risk of developing posttreatment otitis than patients with normal ears, which suggests that fibrosis of previously damaged tissue may be contributory. One or both ears may develop otitis, however, even when uninvolved by tumor.

Usually otitis is transient and results from desquamated cells and debris, and edema of the mucous membrane lining the eustachian tube. Patients complain of a stuffy feeling in the ear and conductive hearing loss. Some cases resolve when oral decongestants are administered, but others require myringotomy, usually within the first year after treatment. It is rarely necessary to perform myringotomy during a course of irradiation, except in the unusual circumstance when patients have pain. Bacterial infection rarely supervenes.

Sensorineural Hearing Loss

Sensorineural hearing loss is a rarely reported complication of ear irradiation; its incidence is unknown, but it may be more common than generally thought. Of 137 patients who underwent nasopharyngeal irradiation at the Massachusetts General Hospital between 1961 and 1969, 7 (54%) of 13 patients who had pretreatment and posttreatment audiometric evaluation were noted to have developed sensorineural hearing loss.[141] Since a selection factor existed (ie, patients who were evaluated were those who were having problems), the incidence of injury could not be established. Hearing losses ranged from 10 dB to almost total deafness; the most profound losses occurred after extremely high-dose treatment (more than 20,000 cGy). Small sensorineural hearing losses were noted during the first few years, but the onset of severe losses was gradual and occurred 3 to 6 years after treatment. Small losses had flat audiometric patterns, whereas the more profound losses were most severe in the high-frequency range. The risk is greater in older patients.[113,141]

Few reports exist of histologic studies of irradiated temporal bone. In an autopsy done at 1 year posttreatment, Leach noted absence of the organ of Corti and atrophy of the spiral ganglion and cochlear nerve.[113] Schuknecht and Karmody described a patient who had temporal bone radionecrosis 8 years after irradiation; autopsy at 12 years showed atrophy of the organ of Corti, loss of some hair cells, atrophy of the basilar membrane, and loss of some of the cells of the spiral ganglion.[180]

Vestibular Disorders

Little is known about the effects of conventional fractionated radiation on vestibular function. Leach described several patients who complained of vertigo in the postirradiation period, some of whom had abnormal results of ice-water caloric tests.[113] In one patient, 1 year after treatment, absence of the macula (of the utricle) and cristae (of the semicircular canals), the structures whose hair cells transmit sensory information by way of the vestibular nerve to the CNS, was noted at autopsy. Vestibular dysfunction has not been reported by any patient receiving incidental irradiation of the semicircular canals at the University of Florida.

The Spinal Cord and Brain Stem

Lhermitte's Syndrome

A transient radiation myelopathy, manifested by Lhermitte's syndrome, or the "barber chair" sign, occurs frequently in patients whose spinal cords are incidentally irradiated. The syndrome was first described during World War I in French military hospitals by Marie and Chatelin, who noted the syndrome in soldiers who had experienced injuries to the head and neck area.[123,124] Similar cases were described by Babinski and Dubois and by Lhermitte himself in 1918.[7,118] The syndrome was first described in association with radiation therapy in 1948 by Boden.[17] The syndrome consists of a momentary, but disturbing, electric-like shock that is triggered by flexion of the cervical spine. The sensation may be limited to the spine, but more commonly it radiates into the extremities, particularly the backs of the thighs. The distribution of the sensation does not correspond with the finite territory of any dermatome. The distribution usually is symmetric, and equal on both sides of the body. Symptoms usually appear 1 to 3 months after completion of irradiation and last from 1 month to as long as 8 or 9 months, with an average duration of 3 to 4 months. The symptoms usually subside gradually. The syndrome produces no muscle weakness or sphincter disturbance, and no accompanying neurologic signs appear. The character, latency period, and duration of symptoms in this radiation syndrome are identical to those that have been described after traumatic injury to the neck.

Lhermitte's syndrome is an early appearing, benign form of myelopathy and should be distinguished from later-occurring, progressive radiation myelopathy. Lhermitte's syndrome rarely leads to progressive cord degeneration and transverse myelopathy. When the syndrome arises soon after completion of irradiation, healing almost always occurs without permanent damage. When the syndrome appears late (9 to 12 months), however, radiation myelitis may follow.[95]

Damage to the posterior columns is thought to be a prerequisite for Lhermitte's syndrome.[26] Jones attributes the transient myelopathy to temporary demyelination.[95] The minimum dose of radiation that produces Lhermitte's syndrome has not been clearly identified, but a spinal cord dose as low as 3000 cGy in 25 fractions over 7 weeks by split-course irradiation to the Hodgkin's mantle field, with both fields treated daily, may produce mild symptoms.

The syndrome is self-limited, reversible, and requires no specific therapy. In two patients who were extremely symptomatic, a cervical collar was used for several

months until symptoms resolved. Patients should be warned about the syndrome so they are not alarmed should symptoms occur.

Transverse Myelitis

Radiation-induced transverse myelitis is a rare complication of brain stem and spinal-cord irradiation. The process almost always is irreversible, and no effective therapy is known. Symptoms and signs of partial or complete transection of the cord appear 6 months to 2 years after irradiation (the earliest reported case occurred 4 months after treatment). The latent intervals tend to be shortest in patients whose spinal cords were retreated, patients whose cords received the highest doses, and possibly, pediatric patients.[1,181]

Typically, patients first develop paresthesia, followed by steadily progressive sensorimotor disturbances, bowel and bladder dysfunction, and paraplegia or quadriplegia. The sensory symptoms usually begin in the lower extremities, then, over weeks to months, ascend to involve the trunk and upper limbs. The initial findings may, therefore, lead one to suspect a lesion lower in the cord.[171] Pain in the neck and arms is sometimes prominent, and the signs are usually asymmetrical at first. Horner's syndrome has been reported in a few patients.[25] Symptoms progress at a variable rate. Although the signs and symptoms may not progress beyond a certain stage, once present, they rarely disappear. The syndrome results in death in about two thirds of patients within 4 years,[182] and the rest usually are severely incapacitated. Involvement of the sphincters implies a poor prognosis.[152] Complete transverse myelitis at the level of the upper cervical cord or brain stem results in death, usually secondary to bronchopneumonia. In published reports, a number of patients with myelopathy developed the Brown-Séquard syndrome, with loss of voluntary movements and Babinski's sign on one side and loss of pain and temperature sensations on the opposite side; in some patients the syndrome remained stable, whereas in others it progressed.

Diagnostic workup should include lumbar puncture (including cytologic study) and myelogram. The cerebrospinal fluid contains no excess of cells. The myelogram and the total protein in the cerebrospinal fluid usually are normal in patients with radiation myelitis, but cord swelling has been reported, with complete blockage of contrast, as well as marked elevations of protein.[68,128,154,216] Cord narrowing on myelography, presumably due to cord necrosis and atrophy, also has been reported.[6,171] Myelography aids in the diagnosis of extradural metastatic compressive lesions; CT scans and magnetic resonance imaging (MRI) help to exclude intradural or intramedullary tumor.[122] Cervical spine roentgenograms help rule out cord injury secondary to bony problems. The differential diagnosis also includes necrotizing myelopathy,[151] vascular lesions, and syphilis.

Boden reported seven cases of brain stem myelitis after irradiation of tumors of the middle ear, nasopharynx, or parotid.[18] The usual time to onset was about 1 year after treatment, and death followed in all patients within 1 to 6 months. The onset may be preceded by acute stomach ulceration. Common signs and symptoms included nystagmus, cranial nerve palsies, ataxia, paralysis, and anesthesia. A common occurrence was unilateral seventh-nerve palsy and contralateral hemiplegia.

The white matter is more susceptible to radiation injury than the gray matter. A notable manifestation of myelopathy is demyelination, which may be due to injury to the oligodendrogliocyte (the myelin-forming cell of the CNS), obliterative changes in small blood vessels, or both.

Time–Dose–Volume Considerations for Spinal Cord Injury

Marcus and Million evaluated the incidence of cervical spinal cord injury in 2901 patients with malignancies of the upper respiratory tract who received radiation therapy at the University of Florida between 1964 and 1987.[121] A total of 1112 patients received a minimum incidental dose of 3000 cGy to at least a 2-cm length of the cervical cord with megavoltage irradiation, and had at least 1 year of follow-up (unless a neurologic complication occurred before 1 year). One year was chosen as the period of minimum follow-up, since about 70% of myelopathies occur between 6 and 12 months. Of the 1112 patients, 788 were observed for at least 2 years and 308 for at least 5 years. Continuous-course, once-a-day treatment was given to 709 patients, 170 received split-course irradiation, and 233 received twice-a-day irradiation (120 cGy twice a day with a minimum 4-hour interval between fractions). Most of the once-a-day patients received treatment at 180 to 200 cGy/d.

Two patients (0.18%) developed radiation myelitis. One had received 4660 cGy at 173 cGy/d (continuous course), and the other had received 4907 cGy at 169 cGy/d (split course).

The incidence of myelitis for patients receiving 4000 to 4499 cGy was 0 of 442; for patients receiving 4500 to 4999 cGy, it was 2 of 471 (difference not significant); and for patients receiving 5000 cGy or more, the incidence was 0 of 75. The occurrence of myelitis did not correlate well with either total dose or fraction size; the results for 879 patients who received once-a-day irradiation by either continuous- or split-course techniques are shown in Table 13-2. A time–dose scattergram for patients who received treatment twice a day is shown in Figure 13-20. None of 233 patients developed myelitis, including 18 who received doses of 5000 to 5400 cGy.

The incidence of myelitis, according to total dose versus length of spinal cord irradiated, is shown in Table 13-3. No obvious pattern of occurrence is seen. Seventy-eight patients received doses of 4500 cGy or greater to 9-cm or longer lengths of the spinal cord without experiencing myelitis.

McCunniff and Liang reported on 144 patients with cancer of the head and neck treated at the Bowman Gray School of Medicine between 1971 and 1980 who, in the course of treatment, received doses ranging from 5600 to 6500 cGy to varying lengths of their cervical spinal cords.[132] Treatment was by split course; a compensating filter was used in most patients to ensure dose homogeneity throughout the treatment volume. Portals included 3.5- to 15.0-cm lengths of the spinal cord. Treatments were administered 5 days each week. The fraction size (to the spinal cord) was usually less than 180 cGy/d. Eighty-two of the 144 patients had follow-up for more than 1 year, and 53 were observed for more than 2 years. Only one patient developed myelitis (6000 cGy at 200 cGy per fraction). Table 13-4 shows the data on 53 patients who were observed for more than 2 years; 52 of the 53 received cord doses 6000 cGy or greater.

TABLE 13-2. Risk of Myelitis According to Total Dose and Dose Per Fraction in Patients Treated With Once-a-Day Irradiation* (No. With Myelitis/No. at Risk)

Dose (cGy)	< 160 cGy/d	160–179 cGy/d	180–189 cGy/d	≥ 200 cGy/d
< 4000	0/57	0/22	0/21	0/6
4000–4499	0/44	0/191	0/91	0/9
4500–4999	1/23	1/119	0/211	0/28
5000–5499	0/1	0/14	0/22	0/12
≥ 5500	0/2	nd	0/3	0/3

nd: no data.

* 709 potients were treated by continuous-course irradiation; 170 patients were treated by split-course irradiation.

Note: University of Florida data.

(Marcus RB, Million RR. The incidence of myelitis after irradiation of the cervical spinal cord. Int J Radiat Oncol Biol Phys 1990;19:5)

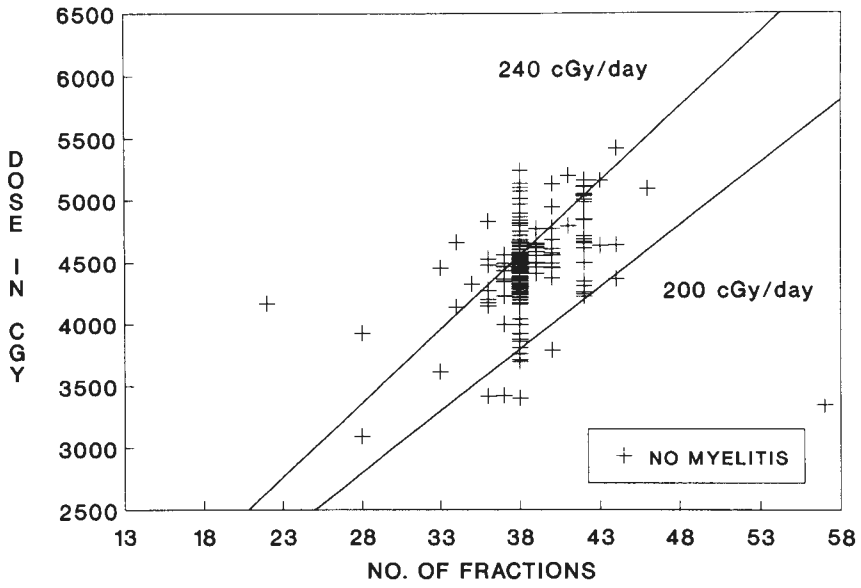


Figure 13-20. Occurrence of radiation myelitis according to cord dose and number of fractions for the 233 patients treated with twice-a-day irradiation. None of the patients developed radiation myelitis. The lines on the graph indicate doses of 200 and 240 cGy/d; they are not isoeffect lines and are for reference purposes only. (Marcus RB, Million RR. The incidence of myelitis after irradiation of the cervical spinal cord. Int J Radiat Oncol Biol Phys 1990;19:6)

TABLE 13-3. Risk of Myelitis According to Total Dose and Length of Cervical Spinal Cord Treated (No. With Myelitis/No. at Risk) (1112 Patients)*

Length of Cord (cm)†	Dose			
	< 4000	4000–4499	4500–4999	≥ 5000
2–4	0/41	0/77	0/85	0/14
5–6	0/51	0/202	1/212	0/31
7–8	0/13	0/94	1/109	0/17
9–10	0/13	0/44	0/54	0/10
>10	0/6	0/25	0/11	0/3

* Includes continuous-course, split-course, once-a-day, and twice-a-day irradiation techniques.

† Lengths were rounded to the nearest centimeter.

Note: University of Florida data.

(Marcus RB, Million RR. The incidence of myelitis after irradiation of the cervicol spinal cord. Int J Radiat Oncol Biol Phys 1990;19:7)

TABLE 13-4. Radiation Myelitis According to Total Dose and Number of Fractions for 53 Patients With More Than 2 Years' Follow-Up

Spinal Cord Dose	Fractions	Average Fraction Size	Patients	Cases of Myelitis
5621	29	192	1	0
6000	30	200	17	1
6000	32	188	3	0
6000	35–37	163–171	3	0
6000	40	150	3	0
6120	34	180	1	0
6331	43	147	1	0
6500	40	163	24	0

Note: Bowman Gray School of Medicine data.

(Modified from McCunniff AJ, Liang MJ. Radiation tolerance of the cervical spinal cord. Int J Radiat Oncol Biol Phys 1989;16:676)

Baekmark reported on 21 patients who had follow-up for greater than 1 year after receiving 5700 cGy over 6 weeks by continuous-course irradiation (five fractions per week); none developed progressive myelopathy.[8] In view of the occasional sporadic appearance of radiation myelitis at low biological dose levels, either some patients must be especially sensitive to radiation effects, or an error has been made in dose delivery; the latter seems more likely. Extension of overall treatment time affords little or no additional protection. Several dose schedules that have been shown to produce a high incidence of radiation myelitis, and which should generally be avoided, are listed in Table 13-5. They all have in common doses per fraction in excess of 200 cGy.[52,66,86]

With conventional fractionation at 180 to 200 cGy/d, five fractions per week, the risk of cord injury at 5000 cGy total dose is nearly zero if only a short segment of the upper cord is irradiated. Generally, the longer the length of cord irradiated, the greater is the likelihood of myelitis.[74] Extension of the lateral portals to cover the entire neck results in irradiation of long lengths of cord and increases the risk of damage. A conservative estimate of the risk of myelitis after 6000 cGy over 7 weeks (five fractions per week) is less than 5%.

Radiation myelitis should remain a rare complication of radiation therapy. Conventional wisdom in some departments says that the TD5/5 (dose after which 5% of patients develop myelitis by 5 years) for spinal cord injury is 4500 to 5000 cGy given over 5 weeks. If this were true, then myelitis would be a common problem, since for many radiation departments several hundred patients a year receive such doses. The occurrence in a department of more than one or two cases every 5 to 10 years in the treatment of squamous cell carcinoma of the head and neck seems to be excessive. From a practical standpoint, however, the tiny risk of radiation myelitis must be explained to patients, since an error in dose delivery never can be excluded.

Guidelines at the University of Florida call for portal reductions off the spinal cord after doses of 4500 to 4680 cGy in 25 to 26 fractions (180 cGy per fraction); 4600 cGy in 23 fractions (200 cGy per fraction); or 4560 in 38 fractions (120 cGy per fraction twice a day). If necessary, the dose to lymph nodes behind the plane of the spinal cord is then boosted with electrons or an anterior and posterior wedge pair, or the nodes are removed by neck dissection.

Higher doses are required, however, in certain circumstances (eg, advanced cancer of the nasopharynx or unresectable sarcomas encircling the spinal canal). In these circumstances, the risk of injury must be weighed against the consequences of uncontrolled tumor growth, and a 5%, or even 10%, probability of spinal cord injury becomes an acceptable risk. It is illogical in such cases to limit the cord dose to 5000 cGy.

Correct diagnosis of the reason for myelopathy is crucial, so that appropriate therapy may be instituted, as illustrated by the following case at the University of Florida.

> The patient was 55 years of age when diagnosed with a T2 N2B squamous cell carcinoma of the right tonsil. He received 6600 cGy in 33 fractions over 62 days, between March 6 and May 11, 1972, by split-course irradiation. The upper (C1–3) cervical spinal cord received 3940 cGy in 20 fractions. The radiotherapy was followed by right radical neck dissection; seven lymph nodes contained cancer, with extracapsular spread. Seven months after treatment, the patient complained of numbness and weakness of the right lower extremity. Over the next week the numbness ascended to include the right trunk and right arm, with right neck pain. There was decreased pinprick sensation throughout the area of numbness, and weakness of the quadriceps muscle on the right. Myelogram revealed diffuse cord enlargement from C3 through C6. Laminectomy revealed diffuse cord enlargement at these levels. Biopsy revealed metastatic intramedullary carcinoma. Over the next week, the patient lost motor and sensory function in his lower extremities and eventually developed quadriplegia. Treatment consisted of palliative irradiation (February 1973). The patient died on July 10, 1974.

The Brain

Adverse effects of irradiation on the brain are divided into three groups, depending on the time of appearance. Acute reactions occur during and immediately after a course of irradiation and consist of edema. In the absence of tumor in the brain, the syndrome is rare and will not be discussed further. The *early delayed* syndrome usually is transient and appears weeks to months after irradiation. The syndrome was first described in 1929 by

TABLE 13-5. Dose-Fractionation Schedules Associated With High Incidence of Radiation Myelitis

Author	Cord Dose	Overall Treatment Time	Dose Schedule	Dose/Fraction
Hatlevoll and coworkers[86]	3800 cGy	5 wk	600 cGy q.o.d. × 3 d, 3-wk split, 2000 cGy in 5 fractions	400–600 cGy
Fitzgerald and coworkers[66]	4000 cGy	5 wk	2000 cGy in 5 fractions, 3-wk split, 2000 cGy in 5 fractions	400 cGy
Atkins and Tretter[6]	1900–2400 cGy	1 wk	2 fractions, 1 wk apart	950–1200 cGy
Dische and coworkers[52]	3350 cGy	2½–3 wk	6 fractions	560 cGy
Abbatucci and coworkers[1]	5400 cGy	6 wk	3 fractions/wk (18 fractions total)	300 cGy
Wara and coworkers[210]	4000 cGy	3 wk	5 fractions/wk continuous course	270 cGy

q.o.d., every other day.

Druckmann,[56] and many names have been applied to it, including early delayed CNS syndrome, transitory CNS syndrome, acute transient leukoencephalopathy, and somnolence syndrome. All apparently describe the same phenomenon. The *late delayed* reaction occurs months to years after irradiation.[187]

Transitory Central Nervous System Syndrome (Early Delayed Reaction)

After irradiation of advanced tumors of the ethmoid or sphenoid sinuses or nasopharynx, about 10% of patients develop a clinically recognizable syndrome characterized by lethargy, nausea, occasional vomiting, headache, and dizziness; rarely, transient cranial nerve palsies or ataxia develops. The syndrome typically appears 2 to 3 months after treatment, lasts 2 to 6 weeks, then disappears spontaneously. Patients should be forewarned of this alarming problem, since it appears about the time that they are beginning to recover from the acute effects of radiation.

The syndrome is believed to result from transient demyelination, secondary to incidental brain irradiation. The latent period corresponds to the turnover time for myelin; the syndrome may be similar in etiology to Lhermitte's syndrome of the spinal cord.[105,188] With the irradiation technique used for tumors of the nasal cavity and ethmoid and sphenoid sinuses, the given dose (at maximum dose [Dmax]) to the anterior portal frequently is about 6000 to 7000 cGy. A substantial volume of brain is incidentally irradiated. When treating advanced nasopharyngeal cancer, portions of the base of the brain, particularly the temporal lobes, may receive very high doses; antral fields add lesser doses to other areas of the brain.

The differential diagnosis usually is recurrent tumor versus delayed transient CNS syndrome, the symptoms and signs of which may be similar. The time frame of CNS syndrome is characteristic, and assists in making the correct diagnosis. Usually no CT scan abnormalities are present, although in one patient, Graeb and coworkers observed low-density changes that subsequently resolved and may have represented the early delayed reaction.[78] Although no specific therapy is required, corticosteroids have been reported to relieve signs and symptoms in severe cases.[59,188]

Because of the transient nature of the early delayed reaction, little information exists on the histologic features. Lampert and colleagues described two patients in whom the early delayed reaction was unusually severe, resulting in the death of both patients.[109,110] Clinically, each case was characterized by the sudden onset of symptoms about 3 months after termination of irradiation. Autopsies showed plaques of demyelination within the field of irradiation that resembled the lesions of acute multiple sclerosis. Also present were perivascular lymphocytic and plasma cell infiltrates. Degenerative vascular changes (which are prominent in the late delayed reaction) were not present.

Late Delayed Reaction

The late delayed reaction usually is irreversible, progressive, and sometimes fatal. Signs and symptoms depend on the area and volume of brain irradiated and resemble those of an intracranial mass.[187] The essential lesion is demyelination with loss of oligodendrogliocytes and focal or diffuse areas of white matter necrosis. Both small-vessel and glial-cell damage are responsible. CT scan demonstrates hypodense areas that are most frequently observed in the periventricular areas, ventricular asymmetry, or dilatation and widening of the subarachnoid spaces (a reflection of cerebral cortical atrophy), and sometimes intracerebral calcification, which represents mineralizing microangiopathy. MRI is better at visualizing the abnormalities than CT scan; white-matter damage is seen as an area of relatively high signal intensity on T2-weighted images. Extensive brain damage is seen as areas of cystic degeneration, representing coagulative necrosis. Most patients whose brains are incidentally irradiated develop no MRI or CT scan abnormalities.[54] Most patients who have mild abnormalities remain asymptomatic, and some with extensive MRI changes also remain asymptomatic. The time interval to the development of frank CNS necrosis is 6 months to 2 years, although occasionally injury is seen later than 2 years.[39] Sequelae consist of impaired mental function in adults, learning disabilities in children, seizures, dementia, and death.

Frank necrosis is rare. Most reported cases have received treatment with large (more than 200 cGy) daily fractions or multiple courses of therapy for cancer of the skin, middle ear, nasopharynx, paranasal sinuses, or primary brain tumors. The incidence of the complication is difficult to determine because literature reports are anecdotal.

Most radiation oncologists regard the maximum safe dose for large-volume brain irradiation in adults to be 5500 cGy in 30 fractions, 5 days per week, over 6 weeks; few data substantiate such a threshold, but the dose is a useful guideline.[16,126] Small volumes of brain tolerate 6000 to 6500 cGy.

Lee and coworkers reported on 9606 patients who received irradiation for nasopharyngeal carcinoma at the Queen Elizabeth Hospital, Hong Kong, 1964 through 1984.[115] One hundred two patients (1%) developed temporal lobe necrosis. The patients received large dose fractions (420 cGy twice weekly to 5040 cGy with or without a boost, or 6000 cGy in 24 fractions at 250 cGy each). Eighty percent of the patients received a single course of treatment, and the rest received a second course of treatment after recurrence. Symptoms included classical temporal lobe epilepsy (déjà vu, hallucinations, or "absence" attacks) in 32 patients; and dizziness, impaired memory, headache, confusion, generalized convulsions, or personality changes in 54 patients. There were no symptoms or signs in 16 patients, although 4 subsequently became symptomatic. The median latency interval for patients who had a single course of irradiation was 4 years compared with 18 months for patients who had two radical courses of treatment. CT scan showed either finger-like hypodense shadows (85 patients) or cysts in the temporal lobes (16 patients). Cerebral angiograms in three patients showed avascular space-occupying lesions with displacement of adjacent blood vessels. Twelve patients had histologic confirmation. Findings consisted of coagulative necrosis, demyelination, fibrinoid changes of blood vessels, hemorrhage, and edema in the white matter. Surgical intervention did not benefit five patients in whom it was undertaken. Seventy-two patients were treated with corticosteroids, and improvement was noted in some patients with early lesions, but not in patients with cystic necrosis.

No specific therapy for radiation-induced brain necrosis exists. Some necrotic foci act like mass lesions; resection of necrotic tissue may be life-saving in this circumstance. Corticosteroid treatment may relieve surrounding cerebral edema.[59] The differential diagnosis includes recurrent cancer and other CNS disease that produces a similar clinical picture.

Cranial and Peripheral Nerves

The cranial and peripheral nerves are seldom regarded as major dose-limiting tissues in treatment planning. Injury is uncommon, even after high-dose therapy. This contrasts to the brain stem and spinal cord, which frequently are the major dose-limiting tissues within a treatment volume.

The most frequent cranial nerve deficit after high-dose irradiation of pharyngeal cancer is hypoglossal nerve palsy.[12,32] Palsy is most likely in patients who develop extensive fibrosis in the neck after high-dose irradiation. The most common scenario is a patient who has a large subdigastric lymph node that has been successfully treated by irradiation alone, who then develops extensive fibrosis, presumably resulting in nerve entrapment and palsy 3 or more years after irradiation. Patients who undergo neck dissection after irradiation are, paradoxically, at less risk of the complication, presumably because the node and its masses of keratin, which eventually is replaced by a fibrous mass,[2] have been removed. Patients who have no lymph node metastasis are at lesser risk of hypoglossal nerve palsy, but occasionally develop the problem if they develop severe fibrosis. Often patients are unaware of the deficit until tongue atrophy, fasciculation, and deviation are noted during a follow-up visit. Speech is not greatly impaired unless both nerves are affected, in which case difficulty in swallowing and aspiration also occur.

No direct treatment for a hypoglossal nerve lesion exists. Dysarthria and problems with voluntary initiation of swallowing are transient. The deficit can be well accommodated, with perhaps only slight dysarthria being detectable. Bilateral hypoglossal nerve palsy can make initiation of voluntary swallowing extremely difficult, requiring alternative feeding methods.[175]

Soft tissue necrosis in the glossotonsillar sulcus may lead to an early appearing hypoglossal nerve deficit, as observed in two patients with cancer of the base of the tongue at the University of Florida. Necroses occurred at 5 and 7 months, respectively, and were followed within 1 month by hypoglossal nerve palsy in both patients; although the necroses spontaneously healed, the nerve deficits persisted. The patients died without evidence of tumor recurrence at 6½ and 8 years, respectively.

Any of the nerves in the parapharyngeal space may be affected, with the vagus and the spinal accessory being next in frequency after the hypoglossal nerve. All three nerves may be involved. Recurrent tumor may produce a similar syndrome, and differential diagnosis is difficult; the timing of the deficit, the absence of other symptoms of tumor recurrence, and the absence of a mass lesion on CT scan or MRI help to establish the diagnosis. Although the facial nerve commonly receives 7000 to 8000 cGy, injury has not been observed at the University of Florida; nor has injury to the olfactory, oculomotor, trochlear, or trigeminal nerves. One patient developed an abducens nerve palsy 10 years after high-dose treatment of an advanced nasopharyngeal carcinoma. Any of the cranial nerves could be affected.

The brachial plexus is included within the treatment volume when the lower neck is irradiated. Elective lymph node irradiation to the lower neck (5000 cGy at Dmax) with an anteroposterior, ^{60}Co portal would produce a dose of 4000 to 4500 cGy to the brachial plexus (at 3 to 5 cm depth, depending on patient's physical structure). Brachial plexus neuropathy is exceedingly rare after standardly fractionated therapy, and has been observed at the University of Florida in only one patient with cancer of the head and neck, who underwent a second course of irradiation for a late supraclavicular nodal failure, which brought the total dose to more than 13,000 cGy. The patient developed marked fibrosis in the supraclavicular fossa with limitation of shoulder and neck motion, painless motor and sensory deficits in the affected arm, diminished brachial and radial pulses, and ipsilateral phrenic nerve palsy, with elevation of the hemidiaphragm.

Most reported cases of radiation-induced brachial plexus neuropathy occurred 6 to 24 months after postoperative irradiation of women with breast cancer. Such injuries are unusual after treatment at 200 cGy/d or less. In the largest reported series, Stoll and Andrews reported on 117 postoperatively irradiated patients who received 480 to 525 cGy three times weekly for a total dose of 5775 to 6300 cGy; 32% of their patients developed neurologic symptoms attributable to brachial plexus neuropathy.[199] The most common symptom was paresthesia; hypesthesia and hand weakness also were common. Examination usually revealed mixed sensory, motor, and reflex changes. The incidence of neuropathy directly relates to total dose and dose per fraction, with a high risk of injury occurring in those whose treatments were administered at 300 cGy or more per fraction (Table 13-6). Breast cancer patients also have had surgical dissection of the axilla before irradiation, which affects the risk of neuropathy.

Anterior Lobe of the Pituitary Gland

The pituitary and hypothalamus are incidentally irradiated during treatment of tumors of the paranasal sinuses and nasopharynx. For many years, pituitary dysfunction after irradiation was thought to be rare. In 1966, Tan and Kunaratnam reported pituitary dwarfism in a young woman who received greater than 9000 cGy for cancer of the nasopharynx at 12 years of age.[201] She stopped growing almost immediately, and developed amenorrhea, hoarseness, and cold intolerance. Examination 11 years after treatment revealed short stature (4 feet 6 inches), small genitalia, underdeveloped breasts, and absence of pubic and axillary hair. There was no evidence of diabetes insipidus. This was the first well-documented case of hypopituitarism secondary to irradiation of an extracranial neoplasm.

Most early observers of pituitary function after irradiation relied on detection of gross clinical abnormalities.[50] Lederman reviewed 241 patients irradiated for nasopharyngeal cancer at the Royal Marsden Hospital (London) between 1933 and 1958, and found no evidence of pituitary dysfunction in any patient.[114] Sophisticated tests (eg, radioimmunoassay and stimulation tests employing synthetic hypothalamic hormones) that were unavailable to early investigators have shown that pitui-

TABLE 13-6. Incidence of Injury to the Brachial Plexus According to Time–Dose Factors (Breast Cancer)

Institution (Author)	Patients	Dose to Plexus (cGy)	No. Fractions	Fraction Size (cGy)	Overall Treatment Time (wk)	Incidence of Plexus Injury (%)
Milan (Basso-Ricci et al.)[10]	200	4900	25	196	5	0
Royal Marsden (Powell et al.)[168]	111	5400	30	180	6	1
Milan (Basso-Ricci et al.)[10]	490	6000	30	200	6	3
Royal Marsden (Powell et al.)[168]	338	4500	15	300	6	6
Ottawa Clinic (McDermot)[133]	21	4000	10	400	4	29
	10	4000	13	308	4	10
	12	4400	13	338	4	17
MacCallum Clinic (Stoll and Andrews)[199]	25	4450	10	445	3	16
	84	5100	11	465	3½	15
	33	5500	12	460	3½	73
Umea, Sweden (Westling et al.)[213]	18	5200	15	347	3	17
	71	5400	17	318	3½	60

tary dysfunction is more common than previously thought. The exact incidence is still unknown, since many of the patients have been selected for evaluation because of some clinical abnormality.

The pituitary of the child is thought to be more sensitive than that of the adult.[72,91] It has also been suggested that female patients are more susceptible than male patients to irradiation-induced hypopituitarism.[107]

Samaan and colleagues studied 110 patients with tumors of the nasopharynx or paranasal sinuses 1 to 26 years after irradiation to portals that included both the hypothalamus and pituitary gland.[177] None had roentgenographic evidence of tumor invading the pituitary fossa; all were free of disease at the primary site. Patients were studied clinically and by biochemical endocrine testing, including tests before and after stimulation with insulin, luteinizing hormone–releasing hormone (LH-RH), and thyrotropin-releasing hormone (TRH). Seventy-six patients (69%) showed one or more features suggestive of hypothalamic injury, and 43 (39%) had evidence of primary pituitary deficiency. The percentage of patients with clinical and biochemical abnormalities increased as a function of time up to 10 years after treatment. Impairment can be demonstrated as early as 1 year after irradiation.[108] Other authors have similarly concluded that the hypothalamus more often is the site of injury than the pituitary gland.[91,108,185]

Growth Hormone

Growth hormone (GH) is the hormone most frequently affected by hypothalamic–pituitary irradiation[72,211] and often is the first deficiency to occur.[108] The secretion of GH is episodic, and its serum concentration is affected by sleep, eating, stress, exercise, and various other stimuli. Demonstration of a low serum level is not sufficient to make a diagnosis of GH deficiency; inability of the pituitary to respond to one of various stimuli, including insulin-induced hypoglycemia, L-dopa, and arginine, must be demonstrated. Samaan and colleagues detected subnormal serum GH levels during insulin-induced hypoglycemia in 56 M.D. Anderson Hospital patients; 21 prepubertal patients showed growth failure and delayed bone age.[177] At the University of California, San Francisco, nine patients who had received incidental pituitary irradiation (3850 to 5700 cGy) during childhood were referred for evaluation of growth retardation.[211] All nine demonstrated GH deficiency after stimulation testing; the intervals between irradiation and evaluation ranged from 1 to 7½ years.

Shalet and coworkers noted subnormal responses of GH after insulin in 14 of 17 children who received 2500 cGy in 10 fractions over 2½ weeks for leukemia.[185] Despite biochemical evidence of impaired GH secretion, none of the children had significant bone-age or growth retardation. The authors concluded that only a minority of children who were previously irradiated for leukemia became clinically GH deficient and therefore were likely to benefit from GH therapy, despite the finding that most had reduced GH responses to pharmacologic stimuli. Their recommendation for such children is the same as for any child with a potential growth disorder, that is, to measure the growth rate at regular intervals and test for GH secretion only if the rate declines significantly. Duffner and colleagues recommend that if children's growth decelerates to less than 4 cm per year, tests of GH secretion are indicated.[57] Hormonal deficiencies may be treated successfully with replacement therapy, but must be detected before epiphyseal fusion occurs.

The diagnosis of GH deficiency in an adult is of academic interest only, since the hormone need not be replaced.

Corticotropin

Measurement of corticotropin (ACTH) plasma concentration is of little value, since daily levels fluctuate markedly. Even healthy patients may have levels below detectability.

In our own clinic, the serum morning cortisol is used to screen patients for more sophisticated testing, such as cortisol response to insulin-induced hypoglycemia.

Samaan and coworkers found 30 patients who showed a subnormal rise of plasma cortisol during insulin hypo-

glycemia. Twenty-two complained of weakness and fatigue, whereas eight others had symptoms of severe deficiency (epigastric pain, diarrhea, hypotension, and drowsiness) which responded promptly to cortisol administration.[177] Addisonian crisis rarely is seen.

Correction of the metabolic derangement is readily achieved with oral replacement therapy. Mineralocorticoid hormone therapy seldom is necessary.

Gonadotropins

The anterior pituitary secretes two gonadotropins, follicle stimulating hormone (FSH) and luteinizing hormone (LH), which regulate the development, reproductive functions, and hormonal secretions of the testicle and ovary. The screening test for gonadotropin insufficiency in male patients is serum testosterone. In female patients, basal and stimulated (LH-RH) FSH and LH values are obtained.

Samaan and coworkers noted subnormal LH and FSH levels before and after administration of LH-RH in 33 patients, indicating a primary pituitary deficiency.[177] Signs and symptoms included amenorrhea, impotence, absence of pubic and axillary hair, testicular atrophy, and decreased libido.

Estrogen or testosterone therapy is done under the direction of an endocrinologist.

Thyrotropin

Hypothyroidism may result from irradiation of the thyroid (primary hypothyroidism) or pituitary (secondary hypothyroidism) gland. Twenty-one patients from the M.D. Anderson Hospital had low thyroid function and thyrotropin levels that were not elevated and failed to rise after administration of TRH, indicating pituitary deficiency.[177] Nine others with low thyroid function had low thyrotropin levels that showed a delayed rise after TRH administration, suggesting a hypothalamic problem. If primary hypothyroidism had existed, high thyrotropin levels due to loss of the normal feedback mechanism would have been expected. Symptoms and signs included cold intolerance, dry skin, constipation, and slow relaxation of tendon jerks. Hypothyroidism is controllable with replacement therapy.

Prolactin

Prolactin secretion is under the inhibitory control of the hypothalamus. In the presence of a hypothalamic lesion, the basal serum prolactin level is elevated. Forty-three of 110 patients from the M.D. Anderson Hospital showed hyperprolactinemia, presumably from hypothalamic injury.[177] Amenorrhea and galactorrhea resulted.[91,107]

Follow-Up Policy

A routine follow-up policy for patients whose pituitary–hypothalamic axis was irradiated has been instituted at the University of Florida. Adult patients are asked about impotence, libido, amenorrhea, oligomenorrhea, and galactorrhea. Children are observed by a pediatrician, who looks for evidence of decline in growth rate.

Annual evaluations of thyroxine (T_4), thyroid stimulating hormone (TSH), and serum morning cortisol are performed in all patients. Testosterone levels are checked annually in male patients. FSH and LH are checked in postmenopausal women. If any test results or symptoms suggest deficiency, patients are referred to an endocrinologist for detailed evaluation.

The Posterior Lobe of the Pituitary Gland

Diabetes insipidus has been reported after deliberate pituitary ablation by transsphenoidally implanted yttrium-90 pellets, which deliver tens of thousands of centigrays to the pituitary gland. The complication is not reported after standardly fractionated radiation therapy.

Thyroid Gland

Clinical hypothyroidism develops after lower neck irradiation in about 5% of adults and a somewhat higher proportion of children. The problem is more common in women than men.[167,207] Signs and symptoms may be classic, but often are nonspecific and attributable to other causes. The chemical detection of hypothyroidism can be made some weeks before clinical symptoms or signs develop. Onset of hypothyroidism may occur within weeks of the completion of treatment but more often occurs months or years later. Frequency of development apparently is related to dose as well as to volume[38,75]; the isthmus of the gland should be shielded during lower neck irradiation, if practical to do so. The addition of a hemithyroidectomy after irradiation increases the risk of subsequent hypothyroidism.[153,207]

The screening test is the serum T_4 level. A high serum TSH level confirms the diagnosis of primary hypothyroidism.

The incidence of chemical hypothyroidism, as manifested by elevated TSH levels with normal T_4 levels, has been estimated to be as high as 20% to 25% after radiation therapy for cancer of the head and neck.[167] The addition of hemithyroidectomy increased the incidence to 66% in the series by Vrabec and Heffron.[207] The condition may represent mild or developing hypothyroidism that has been compensated by increased TSH secretion. In some patients, TSH levels are only transiently elevated and return to normal[38,75,184]; other patients remain euthyroid for long periods while the serum TSH level is persistently high; and others develop frank hypothyroidism. Vrabec and Heffron noted that approximately one third of patients with elevated TSH levels after irradiation alone had depressed T_4 levels. Two thirds of the group with elevated TSH levels after hemithyroidectomy plus irradiation had depressed T_4 levels.[207]

Management of hypothyroidism consists of thyroid hormone replacement. Patients with compensated hypothyroidism (elevated TSH, normal T_4 levels) present a treatment question, since the long-term effects of this condition are unknown. As a minimum, such patients should have their TSH and T_4 levels checked at regular intervals; some authors advocate replacement therapy. The possibility exists that thyroid neoplasia may be induced in these patients secondary to prolonged TSH stimulation, as has been observed in some animals.[72]

Parathyroid Glands and Parafollicular Cells

Serum calcium concentration is maintained in part by the interaction of parathormone (which is secreted by the parathyroid glands) and calcitonin (which is secreted by the parafollicular cells of the thyroid gland). Several retrospective studies have shown that decades after low doses of external irradiation to the neck, the prevalence of hyperparathyroidism is increased.[204] Few data exist on the effect of higher radiation doses. Disorders of calcium and phosphorus homeostasis secondary to irradiation of these structures have not been noted in the University of Florida radiation series. Holten and Peterson studied serum levels of calcium, phosphate, and parathyroid hormone before, during, and every 3 to 6 months after treatment for 3 years in 29 patients whose parathyroid glands received 3700 to 6700 cGy; serum levels of parathyroid hormone showed a slightly increasing trend during the follow-up period. No patient developed hyperparathyroidism, and there was no essential change in serum calcium concentration.[89]

A few reports have been made of parathyroid insufficiency after treatment with iodine-131 (^{131}I) for hyperthyroidism, suggesting that very high doses are required to impair function of the glands.[88]

The Lung

After low neck irradiation, fibrosis of the apical segments of the lungs frequently is seen on routine follow-up chest roentgenograms, beginning 6 to 12 months after treatment. Fibrosis of the apices is of little functional consequence and produces no dyspnea, since these areas of the lung are poorly perfused and ventilated. The apical changes occasionally may be misinterpreted on lung radiographs as mass lesions.

Chronic Lymphatic Obstruction, Lymphedema, and Erysipelas

Irradiation or neck dissection may produce chronic obstructive lymphedema that predisposes patients to erysipelas. Erysipelas follows large-field irradiation of nasopharynx cancer in about 10% of long-term survivors; it is seen less often after irradiation of other primary sites. The addition of a neck dissection increases the risk. Only 1 of the first 356 patients with 2 years' minimum follow-up who received twice-a-day irradiation for tumors of the larynx, oropharynx, or hypopharynx at the University of Florida developed erysipelas. The condition usually develops months or years after treatment, but rarely, it has been seen during a course of treatment. The infections are similar to those occurring in edematous extremities after axillary or inguinal lymphadenectomy and irradiation. Some patients have repeated exacerbations. Group A β-hemolytic *Streptococcus* usually is the responsible organism.

Onset of the skin infection is abrupt; sometimes a history of an earlier upper respiratory tract infection exists. Although the infection initially is limited to the irradiated fields, it may later extend to unirradiated skin. The skin is hot, bright red, tense, and slightly raised. Fever, chills, and rarely, severe toxemia may occur. The infection typically spreads rapidly behind a well-demarcated border. Appropriate antibiotics are started without delay and usually without obtaining a culture. The disease process generally is rapidly reversed. Older or debilitated patients may become severely, systemically ill and require hospitalization and intravenous antibiotics.

For a detailed discussion of the acute and subacute effects of radiation on the lymphatics, see Chapter 6.

Paranasal Sinuses

After high-dose irradiation of cancer of the nasal cavity and ethmoid and sphenoid sinuses, 5 (10%) of 48 patients at the University of Florida had one or more episodes of purulent sinusitis, unassociated with tumor recurrence.[162] One patient required nasal antrostomy at 16 months, after antibiotics failed to control infection. Another, who had intermittent episodes of purulent sinusitis, developed meningitis 4½ years after treatment. A third developed a 3-mm, asymptomatic fistula between the ethmoid sinus and anterior facial skin 7 years after treatment. A fourth underwent a negative Caldwell-Luc procedure to rule out recurrence 2 years after treatment, whereas the fifth was successfully treated with antibiotics alone.

Patients typically exhibit a purulent nasal discharge, headache, tenderness and pain over the sinus area, facial edema, conjunctival edema, and low-grade fever. The sinus does not transilluminate. CT scan shows opacity. The differential diagnosis is recurrent cancer. Exploration is required for diagnosis and drainage if response to antibiotics is incomplete.

When the sinuses are uninvolved by neoplasm, it is distinctly unusual for patients to develop radiation-induced sinusitis.

Large Arteries

Radiation-induced carotid artery disease is regarded as a rare phenomenon, and its incidence is unknown for the following reasons:

- Few case reports that have clinicopathologic correlation exist.
- Irradiation is delivered at an age when atherosclerotic disease of carotid arteries is common.
- Most reported cases of radiation-induced injury have occurred after a latent interval of 5 to 10 years or more, making an extended follow-up period mandatory to assess the risk.
- Carotid narrowing may be clinically silent in the presence of good collateral flow.

Elerding and colleagues found a nonsignificant (P = .39) trend toward an increased risk of stroke in 910 patients who had received irradiation to at least one entire side of the neck, and who survived a minimum of 5 years after treatment of lymphoma or cancer primary to the head and neck.[61] No apparent correlation between dose and incidence of injury existed.

Piedbois and coworkers reported on five patients who developed carotid artery narrowing or occlusion 3 to 11 years (mean, 6 years) after irradiation for cancer of the head and neck.[166] All five patients had other atherosclerotic risk factors (smoking in five, hyperlipidemia in two, diabetes and high blood pressure in one); two of the pa-

tients had no significant arterial disease outside of the irradiated area. Stenoses were treated by bypass (four patients) or endarterectomy (one patient). One patient had to have reoperation 5 years later because of stenosis of the bypass. Functional results in the other four patients remained satisfactory at 3 to 7 years. Anastomotic leakage and cutaneous nonhealing were not encountered.

Histologic changes include intimal thickening with or without superimposed thrombus, fragmentation of the internal elastic membrane, atheroma formation, fibrosis of the media, and adventitial fibrosis. Atheromatous narrowing may involve portions of the great vessels not usually involved with atherosclerosis.[190]

Vascular reconstruction may be indicated. After moderate doses (4500 to 5500 cGy) at Stanford University (Stanford, CA), carotid endarterectomy was technically more difficult than in unirradiated patients, but it was accomplished without increased morbidity or mortality.[190] Although one might suspect that higher doses would significantly increase the operative risk, several patients from the University of Florida have undergone endarterectomy in heavily irradiated necks without serious complications.

In one heavily irradiated patient (dose unknown), Levinson and coworkers at the University of California, San Francisco, performed bilateral carotid endarterectomies and successfully bypassed both common carotid arteries from the level of the clavicle to the bulb by means of saphenous vein grafts.[117] The only bypass reported by the Stanford group (after 12,000-cGy skin dose) was unsuccessful due to clot formation.

Percutaneous transluminal angioplasty has been used to recanalize heavily irradiated brachial and iliac vessels in a limited number of patients.[80,176] The technique avoids a surgical procedure in heavily irradiated tissue. Although we are not aware of patients who have undergone transluminal angioplasty for postirradiation carotid injuries, it could be considered.

Arterial rupture after irradiation fortunately is rare; rupture usually is precipitated by wound complications (necrosis, infection, dehiscence, or fistulae) after operation. Ruptured vessels show transmural necrosis of the vessel wall. The complication is dramatic and often fatal.[64]

Call and coworkers described carotid artery thromboses in three young patients (26 to 42 years of age) after 3800 to 7000 cGy.[27] In each instance the occlusion occurred within 3 years postirradiation in the absence of atherosclerotic stenosis. The authors speculated that this earlier-appearing type of injury resulted from intimal damage, and suggested that patients who develop neurologic symptoms or signs after neck irradiation should be evaluated for carotid or vertebral artery disease regardless of age, radiation dose, or interval from irradiation. If the ischemic nature of the symptoms appears definite, antiplatelet agents are recommended even if vascular studies are negative. If symptoms persist, the authors recommend consideration of antithrombotic therapy with warfarin.

Radiation-Induced Neoplasia After Therapeutic Irradiation

The carcinogenic effect of ionizing radiation has long been recognized. The first case of a radiation-induced malignancy was reported in 1902, an epidermoid carcinoma on the hand of a radiation technician. Despite extensive use of therapeutic irradiation for cancer of the head and neck, induction of malignancy fortunately is rare. Most reported cases have been sarcomas, usually osteogenic sarcomas or fibrosarcomas of bone, and less often soft tissue sarcomas.

The latent interval between irradiation and the development of cancer varies from several to many years. To qualify as a radiation-induced cancer, histologic proof must exist of a new cancer and the lesion must be within the prior field of irradiation. Three aspects of the problem of radiation-induced neoplasia are explored: mucosal lesions, primarily squamous cell carcinomas; sarcomas; and thyroid neoplasia.

Radiation-Induced Mucosal Cancer

In 1975, Lawson and Som analyzed 535 patients who had follow-up for 5 to 25 years after treatment of T1 vocal cord cancer by cordectomy or hemilaryngectomy (310 patients) or by irradiation (225 patients).[112] Twelve (4%) of the surgery group and 18 (8%) of the radiotherapy group developed second primary laryngeal carcinomas ($P = .017$). Since their study, a large body of data from a number of institutions has failed to confirm the authors' conclusions that irradiation is likely to result in a higher incidence of subsequent cancer.

In a 1982 review of more than 200 cases of laryngeal cancer with more than 5 years' follow-up after irradiation, Harwood and Yaffe found no such excess risk.[84]

At the M.D. Anderson Hospital, Kögelnik and colleagues reviewed the late clinical courses of patients who had received curative therapy for head and neck squamous cell carcinoma and lived for a minimum of 5 years without recurrence of cancer within that 5-year period.[103] The clinical occurrences subsequent to 5 years were recorded in 1163 patients after surgery, irradiation, or combined treatment. Follow-up intervals ranged from 7½ to 25 years. The incidence of new cancer developing in the original disease site, the immediate vicinity of the original lesion, or sites remote from the primary lesion but still within the oral cavity and pharynx was not higher in the group who received irradiation alone or irradiation plus surgery when compared with patients who received operation alone. It was concluded that irradiation did not produce an excess of new squamous cell carcinomas compared with surgery.

Data from the Fox Chase Cancer Center, Philadelphia, on almost 2000 patients who underwent surgery or irradiation for cancer of the oral cavity or oropharynx, showed a slightly higher incidence of new upper aerodigestive cancer in the surgery group.[183]

Parker and Enstrom evaluated 2151 patients for second primary malignancies of the head and neck after treatment of their first cancer of the head and neck at University of California, Los Angeles, between 1955 and 1979.[156] Follow-up ranged from 5 to 30 years. No significant difference in the risk of developing a second cancer was noted in the group treated by irradiation compared with those treated by surgery.

Friedman and coworkers reported on 1856 patients with head and neck squamous cell carcinomas other than skin cancer who received treatment at the University of Illinois (Urbana, IL) between 1960 and 1980.[71] Four hundred twenty-two patients had follow-up for over 5 years. The incidence of second primary malignan-

cies of the head and neck mucosa did not differ significantly between the groups treated by surgery, irradiation, or surgery plus irradiation.

It has been suggested that irradiation is contraindicated in cancer of the head and neck in patients younger than 40 years of age because of the risk of radiation-induced malignancy. Harwood and Yaffe reported on 272 patients with cancer of the head and neck who were younger than 30 years old when irradiated at the Princess Margaret Hospital; 58 had more than 10 years (up to 24 years) of follow-up.[84] No second malignancy attributable to irradiation was observed.

Radiation-Induced Sarcoma

The rarity of radiation-induced sarcomas, the long latent period (mean, 10 to 12 years) to their development, and the difficulty in obtaining reliable long-term follow-up data make the task of estimating the true risk of cancer induction difficult.[36] Most series report one or two cases of radiation-induced bone sarcoma per 1000 5-year survivors.[85,165,183,197] Assuming a malignant induction in 1 patient of every 500 long-term survivors, then with an estimated 5-year survival rate of 40% for all irradiated patients with cancer of the head and neck, one case would be induced per 1250 patients treated. The younger the patient, the greater would be the risk of developing a new cancer, since the at-risk period would be longer; whether children are more susceptible than adults to neoplastic induction, as is suspected by many authors, remains unproved but seems likely (see Chap. 32).

Other factors that increase the risk include orthovoltage irradiation, high doses, and multiple courses of treatment spread over many months or years.[84]

Most authors concur that previously abnormal bone, such as that affected by fibrous dysplasia, is more prone to sarcomatous change than normal bone.[35,47,205] Whether the addition of chemotherapy to irradiation increases the risk is unknown; the fact that the only two cases of sarcoma after irradiation of nasal cavity or sinus cancer at Thomas Jefferson University, Philadelphia, developed in patients who had received concomitant chemotherapy is suggestive, but certainly not conclusive, of an increased risk from combined therapy.[35]

Most radiation-induced sarcomas are diagnosed at an advanced stage, have high-grade histologic features, are located where radical surgery cannot be performed, respond poorly to chemotherapy, and as a consequence, have a dismal prognosis.[173,192]

Radiation-Induced Thyroid Cancer

An association between radiation and thyroid neoplasia has long been recognized.[58] The latent period usually is 10 to 30 years. The mortality rate from these forms of thyroid cancer is low, and patients essentially have a normal life span. Almost all of the reported cases have followed doses (6 to 1500 cGy) of radiation that are well below the levels delivered for squamous cell carcinomas (5000 to 7000 cGy). Doses above 2000 cGy are associated with a low risk of induction of thyroid neoplasia compared with lower doses of radiation. This is probably because higher doses either completely destroy the follicular cells or, at least, render the surviving cells incapable of division. Such a situation is seen after ^{131}I therapy for hyperthyroidism; many patients become hypothyroid, but few develop thyroid cancer.

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14

TREATMENT PLANNING FOR IRRADIATION OF HEAD AND NECK CANCER

FRANCIS J. BOVA

The planning procedures implicit in the treatments described in this text are explained in this chapter. It is assumed that the reader has a fundamental understanding of medical physics as it applies to radiation therapy.

POSITION

The selection of treatment position depends on the beam-shaping system, the location of the lesion, and the extent of the treatment portals. A single position (supine, lateral, sitting, prone) or a combination of two or more positions may be used. The supine position is the most comfortable and is easily reproduced. The sitting position, although used successfully in some departments, must be used with caution; patients may slump during treatment if not properly stabilized. Both the supine and the sitting position require the use of beam-shaping techniques with the treatment unit in a horizontal orientation. The lateral, or "chicken wing," position, although slightly uncomfortable, permits the treatment unit to be oriented vertically during the treatment of lateral portals. This allows the use of free-standing or stacked beam-shaping blocks (BSBs). The prone position is used occasionally for a posterior boost portal to a neck mass.

Whatever the position, it is important for the patient to achieve the same alignment each day and hold that alignment throughout the time required to treat all portals. It is preferable to treat all portals without having to shift position for each treatment.

In the lateral position, there are two techniques for positioning the head; the simpler is to use two foam wedges, one with an indentation for the head, the other is to adjust the height. If this technique cannot be used, the alternative is a universal adjustable head holder, which allows the head to be leveled after the patient has been positioned (Fig. 14-1). For patients who have problems maintaining the lateral position, sandbags or straps of Velcro hook-and-loop fasteners at the chest and abdominal levels can help stabilize the position.

Customized semirigid positioning aids are used in many clinics; they have been used for 95% of all head and neck treatments at the University of Florida since 1983 (Fig. 14-2).

SHIELDING MASKS

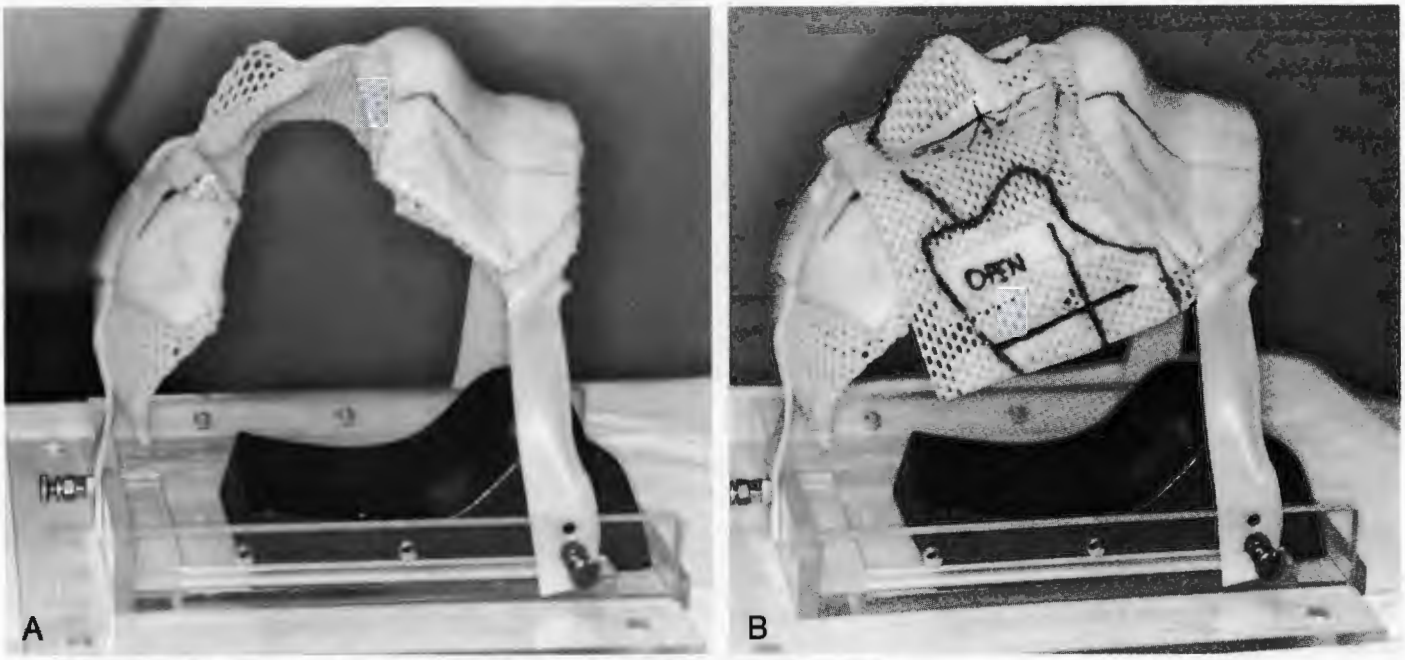
For orthovoltage and small-field electron-beam treatments, it is often advantageous to place the final collimation at or near the skin surface to improve dose distribution at the periphery of the portal. The process is explained in Figure 14-3. The entire procedure requires about 90 minutes and can be performed by one person. It should be noted that adult contours do not vary appreciably, and two or three universal positives can be cast in metal (eg, Lipowitz's metal) and used in almost all routine cases (see Fig. 14-3*E*).

SIMULATION

To design treatment portals from planning films, areas of clinical interest are outlined or marked with radiopaque material. Solder wire can be used to mark lymph nodes of interest, the skin surface, or the location of a portal border that must be determined by physical examination (eg, sternocleidomastoid muscle) rather than from the roentgenogram. For example, the match line between the low-neck portals and the lateral face portals or the posterior neck border of the primary portal can be located and marked. The location of tumor in the tongue, floor of the mouth, or oropharynx can be indicated by stainless-steel pins (Fig. 14-4).

(*text continues on page 297*)

Figure 14-1. The universal headholder is easily adjusted to level the head. Tape is used to reduce head movement. The acrylic base has a tunnel that holds a cassette for localization films. During routine use, a thin foam pad is placed between the patient and the acrylic base for patient comfort. The tip of the nose, the chin, and the suprasternal notch are aligned, usually with the aid of laser lights.



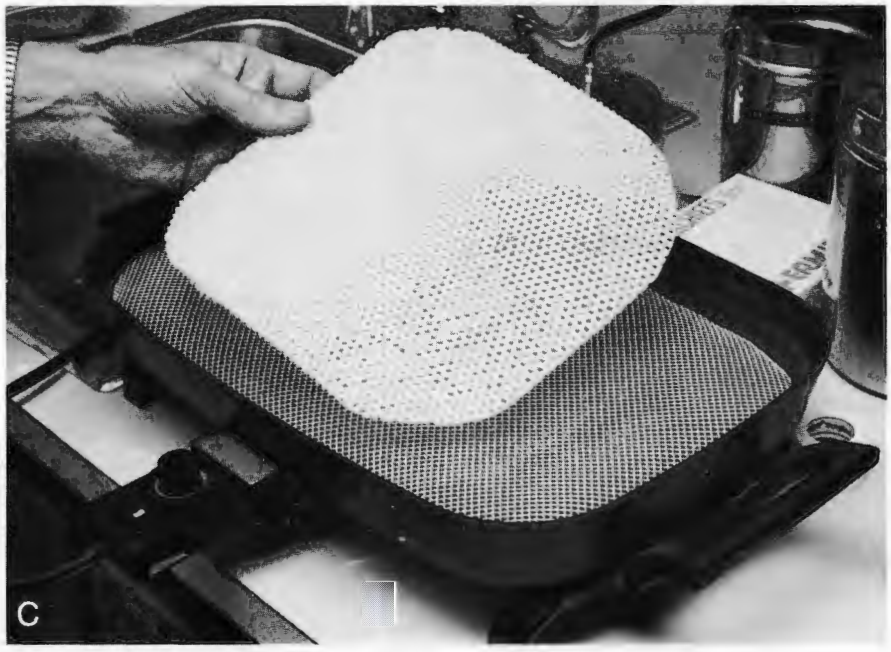


Figure 14-2. (*A*) Customized mask of Aquaplast (low temperature thermal plastic [polycaprolactone]) with acrylic base plate. (*B*) A second mask may be made to aid in beam positioning. The portals are inked on the mask rather than on the patient. This mask is removed before treatment. (*C*) Fabrication of an Aquaplast mask. Aquaplast is cut and placed into a water bath (≈140°). When the Aquaplast becomes translucent and pliable, it is removed from the bath and placed on a towel to dry. Aquaplast adheres to itself while in the pliable translucent state, and care must be taken not to let the sheet fold onto itself. If a larger water bath is used, a full sheet of Aquaplast can be heated. The larger sheet extends to the base plate, eliminating the need for the fastening strips shown in *E*.

Figure 14-2. (*Continued*) (*D*) The patient is placed on the head/neck support and aligned. A ¼-in spacer is placed under the head/neck support to compensate for a 7% shrinkage of the Aquaplast. (This shrinkage occurs in the final stages of cooling and involves the mask and connecting strips. The spacer is removed only after fabrication is complete and the mask has fully cooled.) The heated Aquaplast is removed from the water bath, patted dry, and applied to the patient and pressed to fit. Aquaplast cools quickly and can easily be applied to the skin without discomfort. It takes approximately 5 minutes for the material to return to its hard, opaque form. (*E*) Once the mask has cooled and hardened, 1-in Aquaplast strips are heated and permanently attached to the original mask by firmly pressing together the warm and the cold Aquaplast. The acrylic base plate has been drilled and tapped. Pressing the end of the strip against the acrylic with the fingers (as shown here) produces an indentation on the Aquaplast. The connecting straps are pressed firmly against the screw holes to identify the spot to be punched. If a full sheet of Aquaplast is used, it is similarly extended to the base plate and pressed against the screw holes. (*F*) The holes are made in the strips with a ¼-in hole punch. The process requires about 20 minutes to this point. The patient is then ready for simulation. (*G*) After the treatment portals have been decided and the beam-shaping block has been fabricated, the portals are transferred back to the patient's surface and the mask is cut away to preserve skin-sparing.

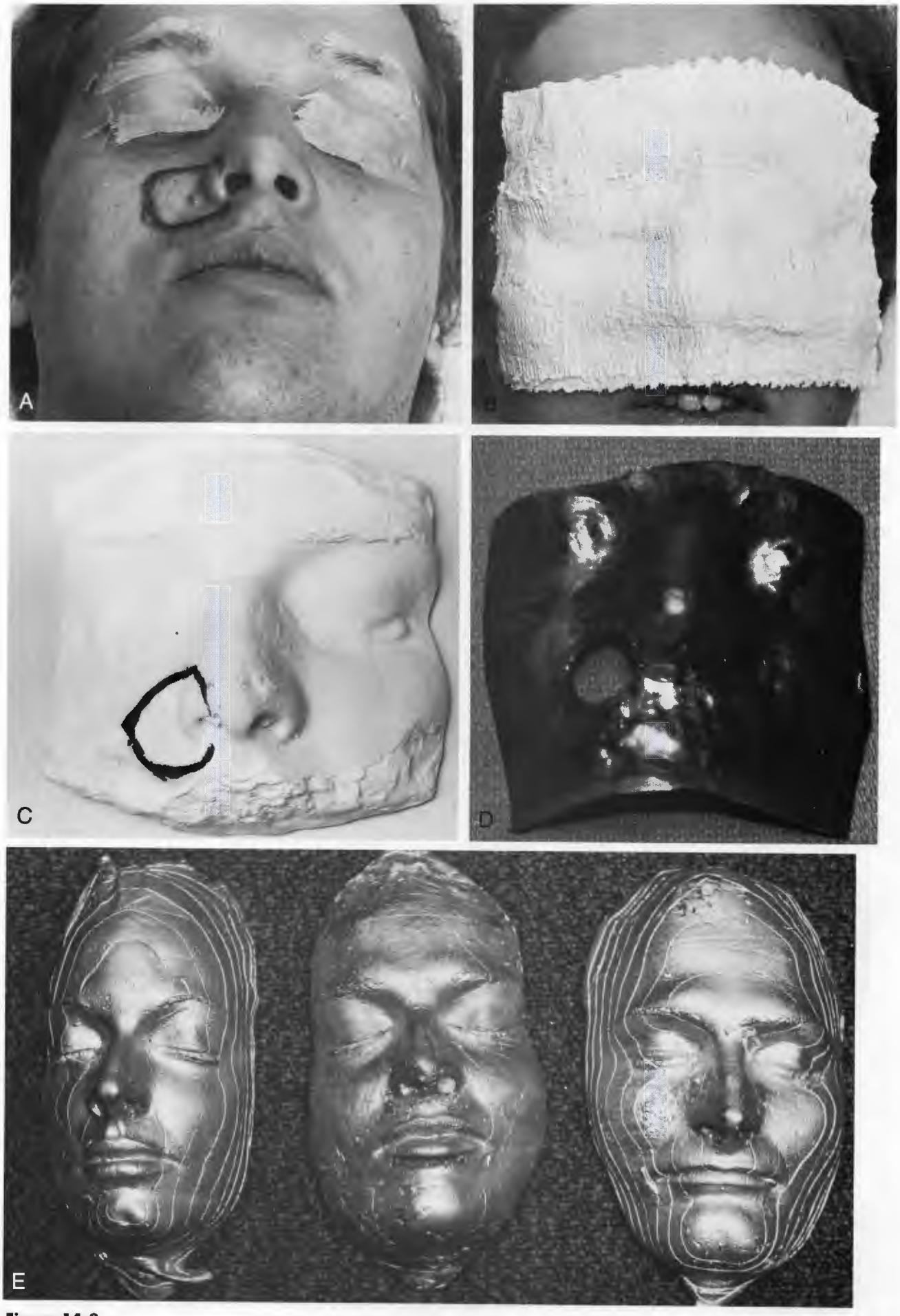


Figure 14-3.

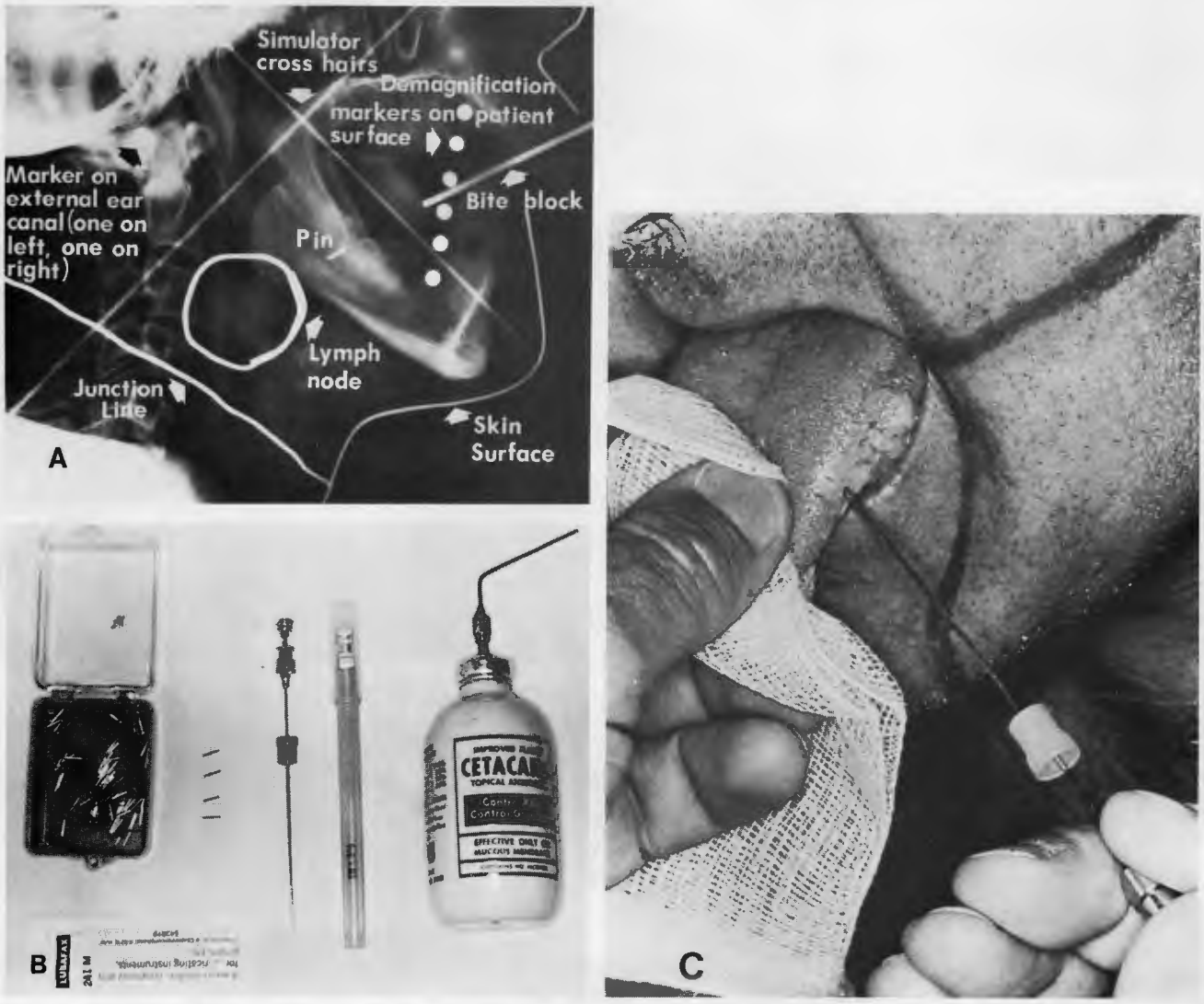


Figure 14-4. (*A*) Simulation film with radiopaque markers to show pertinent anatomy. A lead marker is placed at each external ear canal to gauge rotation of the head and to locate the canals. (*B*) Stainless-steel wire is cut into short segments. After topical anesthesia, a 20-gauge spinal needle is used to insert the pins. The water-soluble lubricant is placed on the pins to help hold them in the tip of the needle. (*C*) Insertion of needle under local anesthesia into the anterior border of an oral tongue lesion.

◄ **Figure 14-3.** Fabrication of a lead mask. (*A*) Step 1. Petrolatum-coated gauze is placed over the eyebrows and eyelashes to prevent plaster from sticking to the hair. The remainder of the skin is covered with a light coat of petrolatum to ease separation of the mask. Cotton may be placed in the nostrils. The treatment portal is outlined in ink and will transfer to the plaster. (*B*) Step 2. Moistened plaster strips are applied to the skin and allowed to harden. (*C*) Step 3. A hard stone positive is prepared, using a material such as white Castone (manufactured by Ranson and Randolf), and the portal is transferred to the positive. Sheet lead (thick enough to reduce transmission to 5% or less) is formed onto the stone positive with a hammer and the portal is cut out. (*D*) A completed lead mask. (*E*) A set of face casts made of low–melting-point alloy. These three casts can be used to prepare lead masks in 95% of cases.

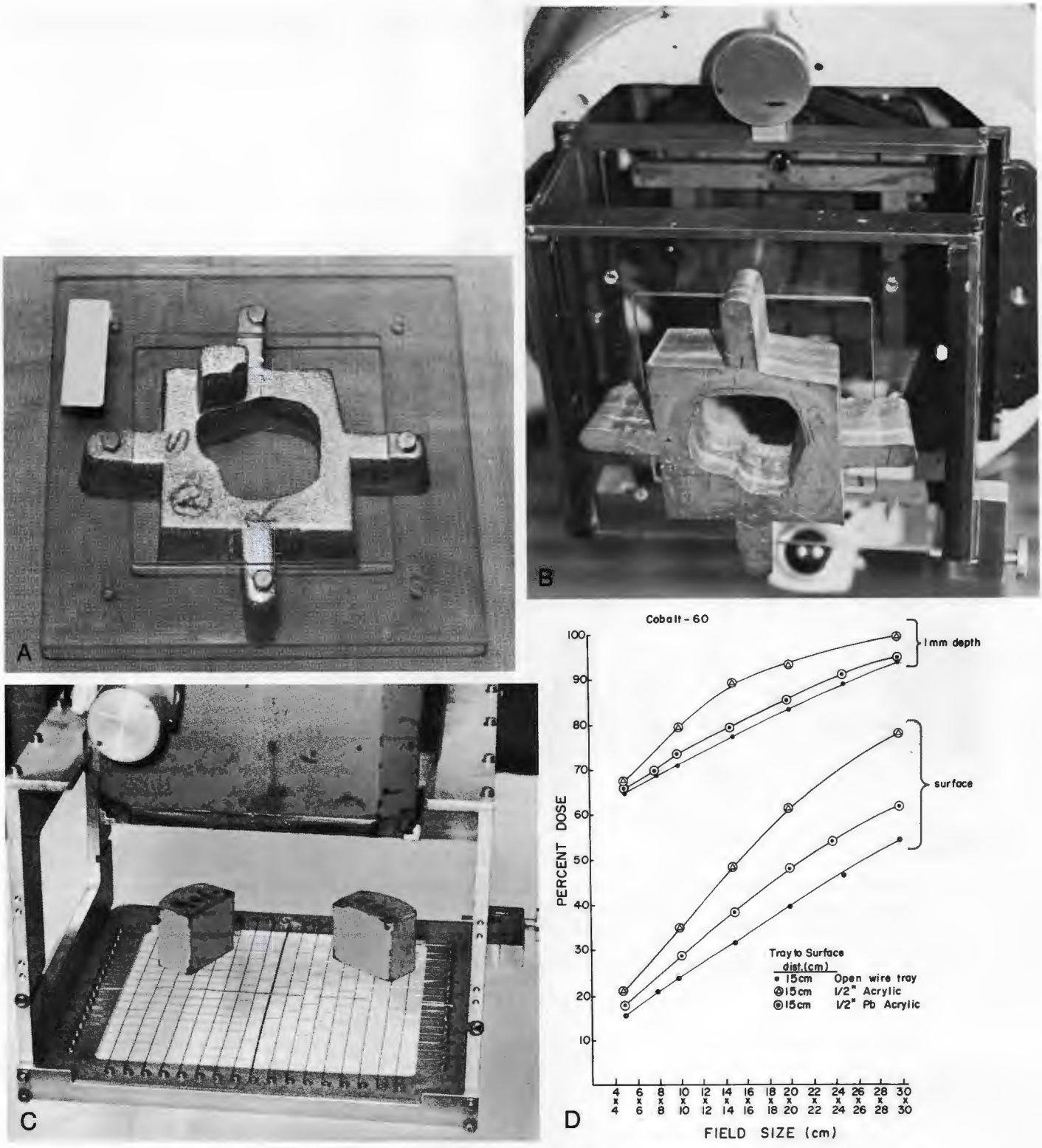


Figure 14-5. (*A*) Head and neck block (3 inches thick) with double-thickness eye block for 8- or 17-MV x-ray. This can reduce the dose to the eye by 3% to 5% compared with single thickness. For a 7000-cGy tumor dose, this is a reduction of 200 to 350 cGy. (*B*) Head and neck block mounted to a treatment unit. The central portion of the Lucite mounting tray has been removed to reduce low-energy scatter to the skin. (*C*) Wire tray for free-hand blocking. Stainless-steel wires, 0.02 inch diameter, on 1-cm centers are used. (*D*) Doses at the surface and at 1 mm for a Picker C-9000, ^{60}Co teletherapy unit. The blocking tray is 65 cm from the source, surface of phantom at 80 cm SSD. *The doses for the wire tray are the same for a 10- to 25-cm tray-to-surface distance.* For example, when parallel-opposed ^{60}Co portals are used to deliver a 7000-cGy midline tumor dose (separation 14 cm), the wire tray would deliver approximately 500 cGy less at 1 mm depth and approximately 700 cGy less at the surface compared with an acrylic tray. These differences are thought to be clinically significant. (*E*) Doses at the surface and at 1 mm depth for a Philips SL75-20, 8-MV x-rays. Blocking tray is 65 cm from target, surface of phantom at 100 cm SSD. (*F*) Doses at the surface and at 1 mm depth for a Philips SL75-20, 17-MV x-rays. Blocking tray is 65 cm from target, surface of phantom at 100 cm SSD. (*E* and *F* from Bova FJ, Hill LW. Surface doses for acrylic vs. lead blocking trays for ^{60}Co, 8-MV, and 17-MV photons. Med Phys 1983;10:255)

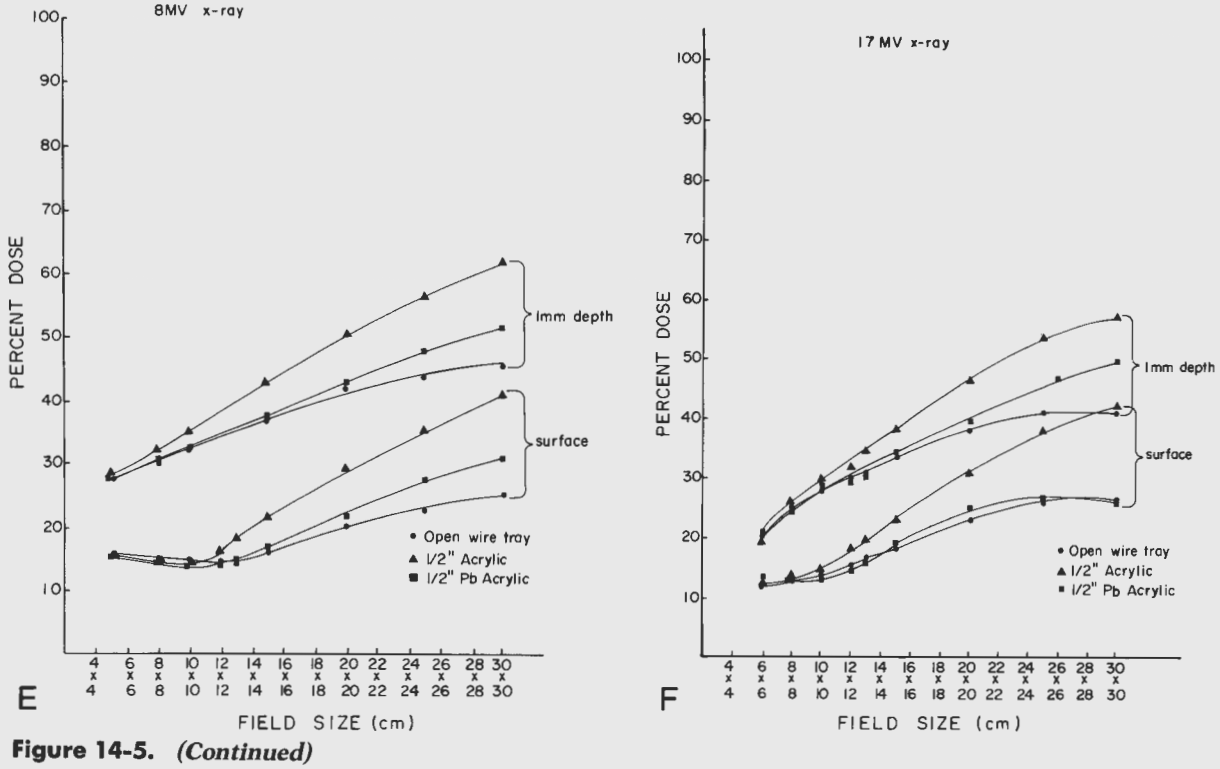


Figure 14-5. ***(Continued)***

BEAM SHAPING

Rectangular beams emanating from the treatment units must be converted into irregular shapes to shield normal tissues. Beam shaping is achieved by two basic techniques: free-style, using stacked lead blocks, and custom-designed, using low–melting-point alloy shields. The advantage of free-style hand blocking is that the set of lead blocks can be used for all patients, reducing costs and simulation time. This system works well for almost all situations but requires the treatment unit to be in a vertical orientation.

Disadvantages of free-style blocking include lack of easy reproducibility and inability to obtain complex free-form portal shapes. These problems are eliminated when custom-designed BSBs are used. Custom-designed BSBs have three major advantages: more normal tissues can be shielded; the patient can easily be treated in the supine position, because the BSBs can be mounted with the treatment unit at any angle; and the portal outline is reproduced precisely each day (although this does not guarantee that errors in daily alignment may not occur). There is a temptation to design the BSB with narrow margins. Not only do these areas require greater precision in daily alignment, but the lack of scatter in these regions can result in areas of reduced dose. Use of custom-designed BSBs also adds to the cost of the treatment, and their fabrication can delay the start of treatment.

One difference between the custom block and the stacked block is the sloping divergent side on custom BSBs versus the vertical side on stacked BSBs. Although the correct divergence is appealing, for small fields (less than 80 cm^2) there exists little physical difference in the resulting penumbra and no clinical difference. It should be remembered that the physical penumbra (the dose gradient at the edge of the portal) as measured by isodose scanning and demonstrated by isodose distribution is substantially altered by minor daily alignment errors and patient motion. The goal in beam shaping is to reduce the transmitted beam to 5% or less of its unattenuated intensity. The thickness of the BSB is usually a compromise between this goal and a practical size for routine use. For cobalt-60 (^{60}Co), the standard lead blocks for free-style stacking have been 3 cm thick, which allows transmission of 15% of the beam; however, because the blocks are used mainly to collimate the edge of the beam, this is a satisfactory compromise. In many situations, lead blocks are stacked in two or three tiers to achieve the proper shape. Blocks that are thicker than 3 cm do not work well in the space available. Critical tissues are double blocked (eg, 6 cm).

Stacked blocks for 8- and 17-MV x-rays are 8 cm thick (5% transmission), which limits the number of tiers that can be stacked. Extra shielding may be added to reduce the dose to a critical structure such as an uninvolved eye. For example, the dose to the eye under a 5-cm alloy block is 10% at 5-mm depth for ^{60}Co. This is partly from transmitted beam (5%) and partly scattered from the treated volume (5%). For a 6000-cGy given dose (D_{max}), the eye would receive 600 cGy from the anterior portal alone. If a 10-cm thick BSB is used, the eye receives only 6% of the given dose to the anterior portal. Similar dose reductions are seen with 8- and 17-MV x-ray beams, which give an eye dose of 9% with 7.5 cm of low–melting-point alloy shielding and 6% with 15 cm of shielding. This reduction may be critical in preventing cataract formation (Fig. 14-5*A*).

There is a difference in skin-sparing depending on the tray used to hold or mount the blocks (see Fig. 14-5*B* and *C*). Secondary scatter from an acrylic tray increases the surface dose and the dose at 1 mm (dermis). The buildup of surface dose versus field size for ^{60}Co, 8-MV x-ray, and 17-MV x-ray beams is shown in Figure 14-5*D* and *E*.[1] For freehand blocks, the standard acrylic tray can be replaced with a wire tray (see Fig. 14-5*F*), whereas for custom blocks, an acrylic tray is used with its central portion removed (see Fig. 14-5*B*). The advantage of the wire tray or the acrylic tray with the center removed for high energies and a 35-cm tray-to-surface distance begins at fields 15 cm in diameter. For ^{60}Co, however, savings can be experienced at 15-cm tray-to-surface distance for all field sizes. Lead acrylic is similar to the wire tray until large field sizes are used and can be used if the strength of a full sheet of acrylic is required (see Fig. 14-5*C* through *E*).

The BSBs are aligned to the patient by mounting the block on the simulator. The BSBs are quickly adjusted under fluoroscopy, and a double-exposure roentgenogram is taken (one exposure with and one without the BSBs). If the simulator cannot accept the weight of the blocks, a lead template (cut from 0.03-inch lead sheet) may be used in place of the BSBs. A third technique is to use the Styrofoam mold that was used to cast the custom blocks; the inside of the mold is brushed with barium, which projects a thin radiopaque line around the proposed portals.

PREPARATION OF CROSS-SECTIONAL OUTLINE

The methods of transferring the patient's cross-sectional outline onto paper (*contouring*) use stiff wire, plaster strips, molding rods, or, more recently, the computed tomographic (CT) scan. The contouring procedure is shown in Figure 14-6. An error in reproducing the surface shape is small compared with errors in diameter. *Attention should be given to anteroposterior, lateral, and triangulation distances.* The levels at which the contours are taken should receive careful thought. For example, the treatment field shown in Figure 14-7 is studied through levels A and B, and two substantially different isodose distributions are obtained. These differences are greater for low-energy photon beams than for high-energy beams and are even greater for electron beams. Therefore, it is advantageous to study several levels through the tumor volume when the treatment portals are al-

Figure 14-6. Procedures for manual contouring. Step 1. Measurements are taken (anteroposterior, lateral, and one or more points of triangulation) and transferred to paper. (*A*) Anteroposterior diameter measured with calipers. (*B*) Measurement from midline to tragus. (*C*) Lateral diameter measured with calipers. (*D*) Transfer of diameters to paper. (*E*) Step 2. A solder wire is molded to the plane of the contour, and the three points of triangulation are marked on the wire. (*F*) Step 3. The contour is transferred to paper, making sure to align the triangulation points. (*G*) Cross section with critical structures identified. The position of the radiation portals is added, and the contour is entered into the treatment planning computer along with the critical structures and the position of the radiation portals.

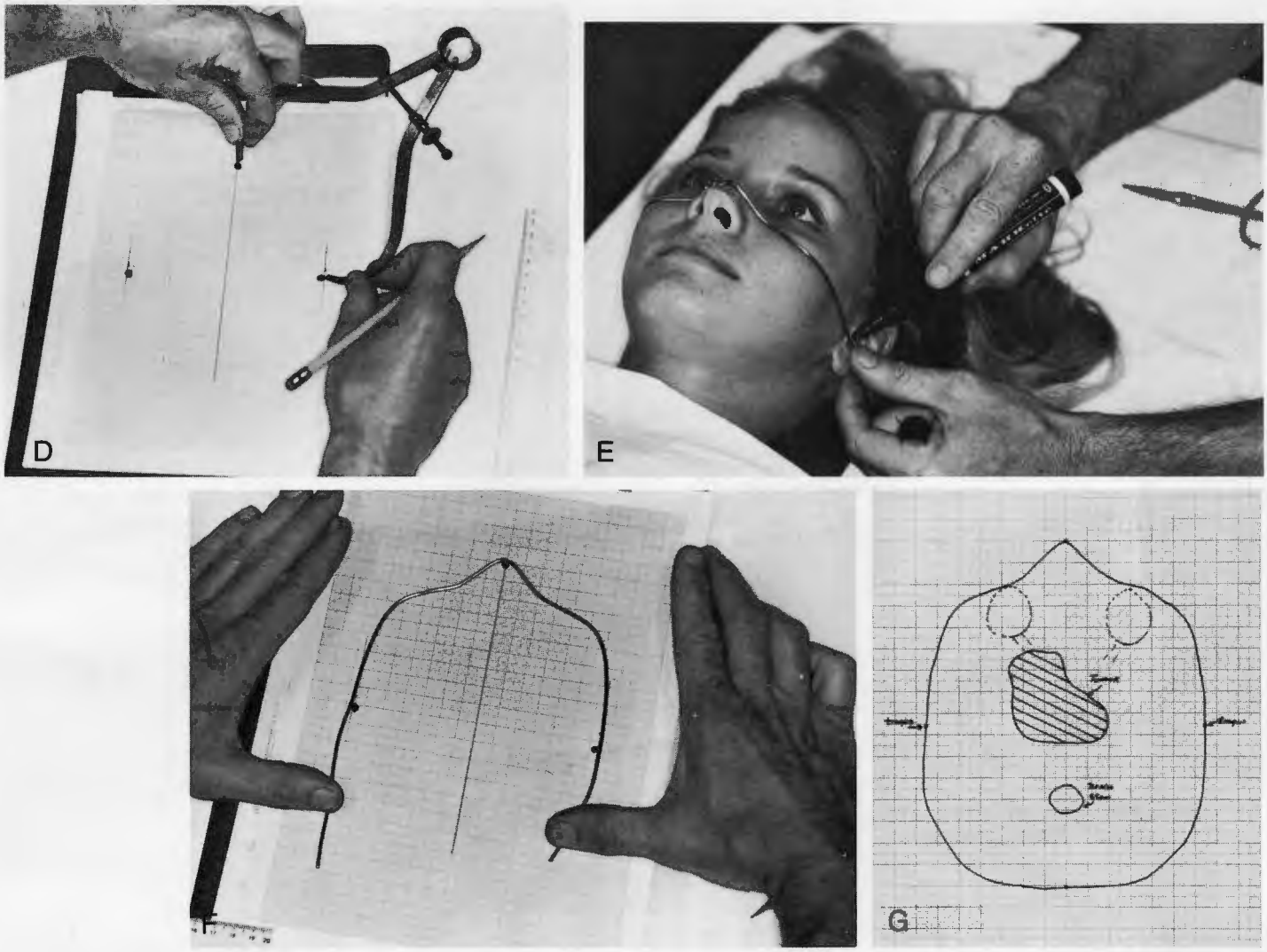


Figure 14-6. ***(Continued)***

tered in shape or where the patient's thickness varies. Additional sections in the coronal or sagittal planes may be useful (see section on treatment planning in Chap. 23).

The idea of CT treatment planning of head and neck targets has found increasing acceptance. For photon beam planning, the main advantage is the overlaying of the dose distribution onto the transaxial CT data. For electron beams, the significant shifts that can result from inhomogeneities can be better appreciated. Unfortunately, algorithms that accurately predict the true three-dimensional effects of inhomogeneities like those found in the head and neck require large amounts of computational time. This results in a trade-off of time for precision in most commercial systems. The clinician should continue to look at electron isodoses with a jaundiced eye.

BEAM CHARACTERISTICS

The characteristics of the available photon and electron beams must be known before treatment planning is started. These characteristics include the buildup region as well as the falloff regions at the edges and deep margins. The buildup region for photons and electrons is highly machine–dependent. The primary collimator and the type of tray used to support collimator blocks affect the surface dose. The buildup curves for ^{60}Co and 8- and 17-MV photon beams are shown in Figure 14-8*A*; those for 6- through 18-MeV electron beams are shown in Figure 14-8*B*.[4] For photon beams, the buildup region extends to greater depths as energy increases, whereas the surface dose decreases with increasing photon energy. Electron beams exhibit just the opposite behavior, with the surface dose increasing as beam energy increases.

Manufacturers routinely specify photon beams by a percentage depth dose at a depth of 10 or 20 cm. For electron beams, either the extrapolated range method or the depth of the 50% ionization point is used to designate beam energy. The buildup region is disregarded for photons and electrons. Therefore, it is possible and likely that two beams of similar energies can differ in surface dose by 10% to 20%. A 17-MeV electron beam from a Philips SL75-20 and a 17-MeV electron beam from a Therac 20 are shown in Figure 14-8*C*. The surface doses are 87% and 82%, respectively. For a tumor dose of 6000

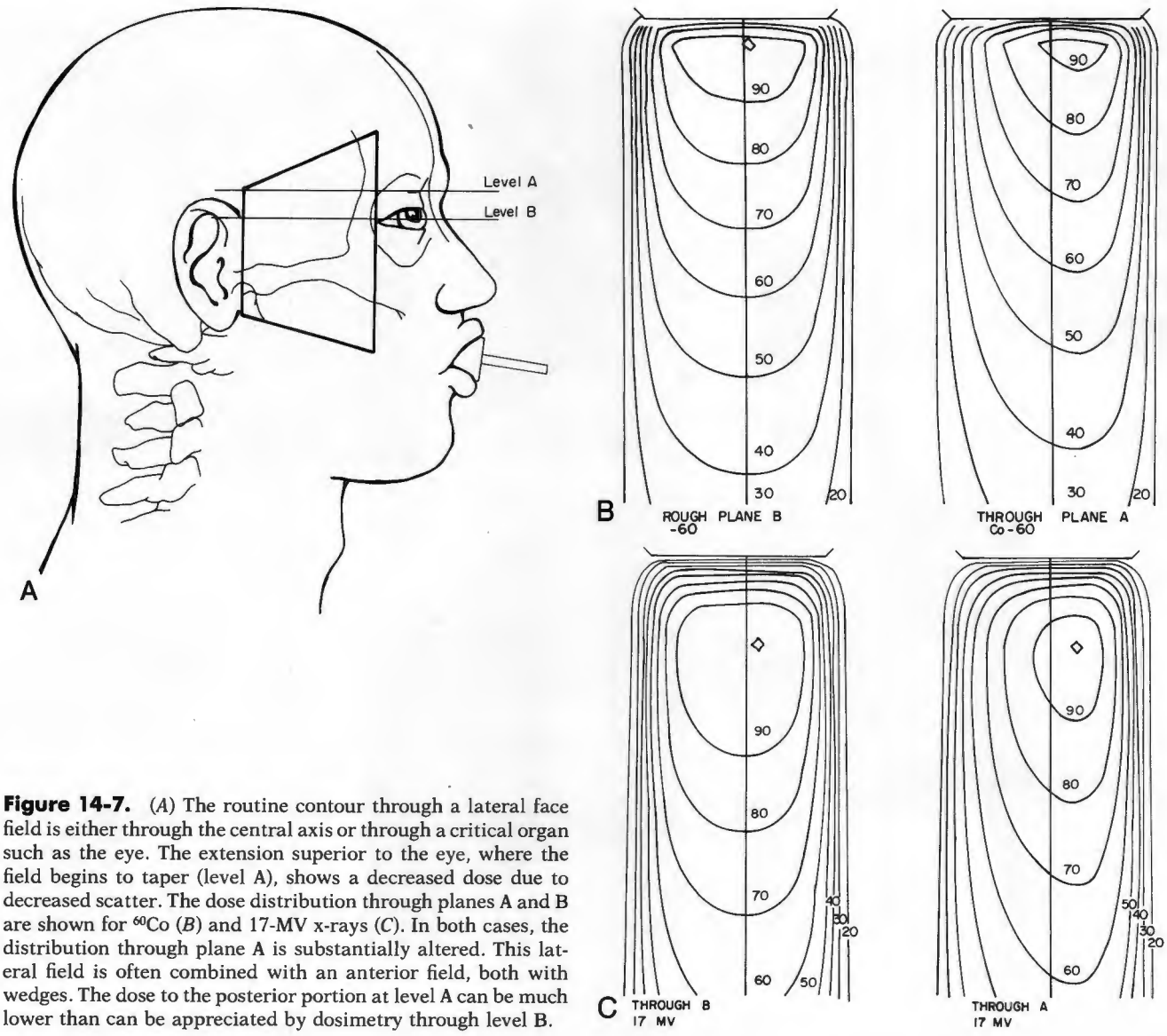


Figure 14-7. (*A*) The routine contour through a lateral face field is either through the central axis or through a critical organ such as the eye. The extension superior to the eye, where the field begins to taper (level A), shows a decreased dose due to decreased scatter. The dose distribution through planes A and B are shown for ^{60}Co (*B*) and 17-MV x-rays (*C*). In both cases, the distribution through plane A is substantially altered. This lateral field is often combined with an anterior field, both with wedges. The dose to the posterior portion at level A can be much lower than can be appreciated by dosimetry through level B.

cGy at the 90% depth dose, the surface dose with the Philips SL75-20 would be 5800 cGy and for the Therac 20, 5460 cGy (a difference of 340 cGy). This might be advantageous or disadvantageous, depending on the tumor location. The depth contained in the 90% to 100% depth dose is also different: Philips SL75-20, 0.3 to 3.9 cm; Therac 20, 0.8 to 5.6 cm. Therefore, it is important when comparing techniques from one facility to another or one accelerator to another to examine the beam characteristics and not simply to use similar nominal energies.

CORRECTIONS FOR INHOMOGENEITY: CT TREATMENT PLANNING

Routine dosimetry is performed assuming homogeneous tissues; structures such as the mandible are ignored. If a dose of 7000 cGy is computed to the tonsillar pillar at 4 cm (assuming homogeneity), the actual dose after correction for 1.5 cm of mandible is as follows:

^{60}Co	6700 cGy
8-MV x-rays	6900 cGy
17-MV x-rays	6900 cGy
17-MeV electrons	6550 cGy
20-MeV electrons	6700 cGy

The difference between 20- and 17-MeV electron beams is the position at which the initial dose is specified. For the 17-MeV beam, the 4-cm depth is equal to the 93% isodose line. Any shift occurs along the steep falloff region of the depth–dose curve. For the 20-MeV beam, the 4-cm depth corresponds to a plateau of the depth–dose curve. A similar shift in depth, therefore, results in a smaller change in dose value.

The correction for bone and air gaps, based on so-called normal anatomy atlases with assumed normal densities, can lead to inaccuracies as large as the assumption of homogeneity; CT scanning, however, can yield not only a precise contour but also an accurate map of the electron density relative to water. The CT treatment-planning technique involves marking the field

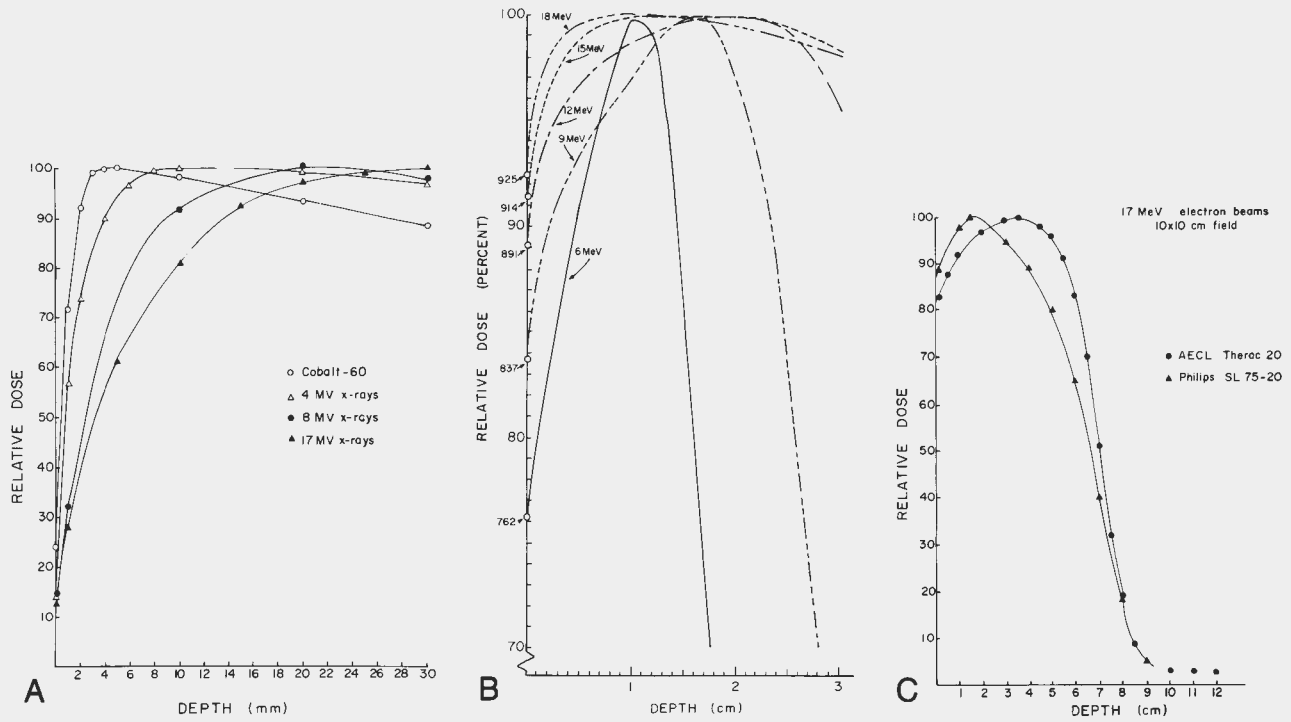


Figure 14-8. (*A*) Buildup curves for 10 × 10-cm field for ^{60}Co, 8-MV and 17-MV photons, and 17-MeV and 20-MeV electron beams. (*B*) Buildup curves for 6-, 9-, 12-, 15-, and 18-MeV electron beams. Cone size is 10 × 10 cm; SSD = 100. (*C*) Electron central axis depth–dose curves for 17 MeV 10 × 10-cm fields for a Philips SL75-20 scattering foil system and a Therac 20 scanning beam system. (*B* from Turner AP. Surface dose measurements of Clinac 18 electron beams. In: Proceedings of the Eighth Varian Clinac Users Meeting, January 31 through February 2, 1980, Kauai, Hawaii)

edges to allow their position to be easily located on the CT slice, reproducing the treatment geometry within the restraints of the CT table and aperture, and being able to remove the artificially imposed CT numbers if a contrast medium has been introduced. Other problems involve attempting to design treatment portals from CT scout views that may not have the correct divergence. The design of a portal from a nondivergent scout view can result in the inclusion in the final portal of critical structures adjacent to the field. If allowance is made for these problems, however, a more accurate dose estimate can be achieved and adjustments can be made for inhomogeneity. CT-based treatment-planning systems are just becoming generally available and will undergo considerable investigation in attempts to improve the delivery of radiation therapy to head and neck neoplasms.

ELECTRON-BEAM DOSIMETRY

Early electron-beam treatment routinely used the 80% isodose level for prescribing the tumor dose; however, this practice should be discouraged. If a tumor dose is prescribed to the 80% isodose value, there is a 20% gradient of dose across the tumor. This is in marked contrast to acceptable external-beam treatment planning, where the tumor volume should be no less than 90% to 95% of the maximum dose, resulting in a 5% to 10% dose gradient. Although prescribing to the 90% to 95% isodose level results in a slightly higher dose to tissue beyond the depth of the tumor, this tissue is still in the declining dose region. This slight increase in dose to the deeper tissue may be a small price to pay for the ability to decrease the given dose by 12.6%; as always, each clinical situation must be evaluated separately.

Prescribing to the 90% to 100% isodose requires consideration of the surface dose. If there is frank tumor at the skin surface or if a surgical scar is present, it may be necessary to apply bolus either to the entire surface or simply the region at risk to obtain a 95% to 100% depth dose. This usually requires 3 to 5 mm of tissue-equivalent bolus. If the region of compensation or bolus is large, the effect on the depth of coverage must be considered. Because of the rapid falloff of electron beams with depth, a small amount of bolus can significantly shift the depth–dose distribution. A second consideration is the size of the radiation portal. If the 90% isodose line is prescribed, the field size must be increased to compensate for the constriction of the 90% and 100% isodose lines that lie inside the physical edge of the beam.

Two or more adjacent electron portals or an adjacent electron and photon portal may be selected in certain situations. The easiest solution is to treat to a common match line and vary the position of the match line one or two times during the treatment course; however, there are common situations when electron portals are used for only 500 to 1000 cGy, and moving match lines is not practical. A common clinical situation is the use of a posterior electron strip to boost the neck nodes behind the plane of the spinal cord. Three examples of the dose distribution for adjacent photon and electron portals are given in Figure 14-9. A small area of high dose is created

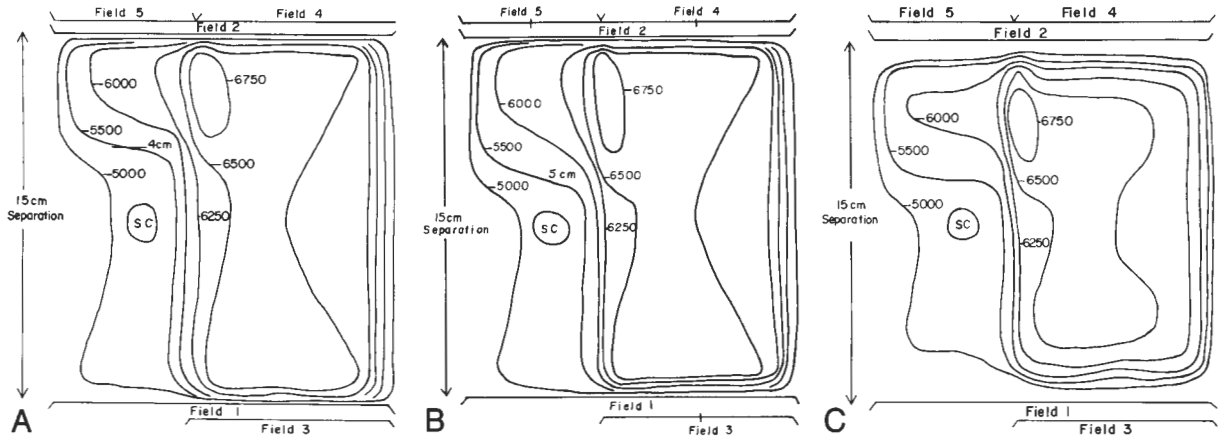


Figure 14-9. Isodose distribution for parallel-opposed photon portals plus one posterior electron strip. When treating a primary lesion to high doses, a reduction is usually planned at 4500 to 5000 cGy to exclude the spinal cord from the field. The dose to the primary lesion is then raised to the final dose (6500 cGy in this example). The dose to the posterior cervical lymph nodes or large lymph node mass is approximately 5000 cGy at this point. Electron fields can be used to increase the dose to these lymph nodes or a mass without increasing the spinal cord dose. (*A*) ^{60}Co parallel-opposed beams (weighted 1 : 1) and 10-MeV electron beam posterior strip.
Fields 1 and 2: ^{60}Co, 12 × 12 cm, SSD = 80 cm, 3495 cGy given dose
Fields 3 and 4: ^{60}Co, 8 × 12 cm, SSD = 80 cm, 1067 cGy given dose
Field 5: 10-MeV electrons, 5 × 12 cm, SSD = 100 cm, 1000 cGy given dose
The electron field is butted against the edge of the photon field (ie, no gap). A small area receives 6750 cGy, which is clinically acceptable. The treatment volume under the electron portal extends from 0.5 to 4.0 cm to a minimum of 5500 cGy, whereas the spinal cord dose is approximately 5200 cGy. (*B*) In this example, the electron-beam energy is increased to 12 MeV and the 5500 cGy lymph node dose is extended to 5 cm, with the spinal cord dose essentially unchanged.
Fields 1 and 2: ^{60}Co, 12 × 12 cm, SSD = 80 cm, 3495 cGy given dose
Fields 3 and 4: ^{60}Co, 7 × 12 cm, SSD = 80 cm, 1067 cGy given dose
Field 5: 12-MeV electrons, 5 × 7 cm, SSD = 100 cm, 1000 cGy given dose
(*C*) In this example, 8-MV x-rays are substituted for ^{60}Co. There is a reduced skin dose, but the distribution is otherwise similar to *B*.
Fields 1 and 2: 8-MV x-ray, 12 × 12 cm, SSD = 100 cm, 2985 cGy given dose
Fields 3 and 4: 8-MV x-ray, 7 × 12 cm, SSD = 100 cm, 900 cGy given dose
Field 5: 12-MeV electrons, 5 × 12 cm, SSD = 100 cm, 1000 cGy given dose

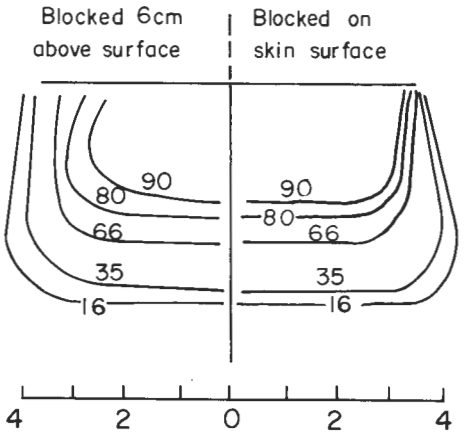


Figure 14-10. A 10-MeV electron-beam portal. A 10 × 10-cm beam is reduced to a 7 × 7-cm field by a lead block. Isodose distribution with block placed on skin surface and 6 cm above the surface (ie, in the electron cone). Note that the effective width for the 90% isodose is 5 to 6 cm for the block on the surface and is reduced to 4 to 5 cm if blocked at 6 cm above the surface.

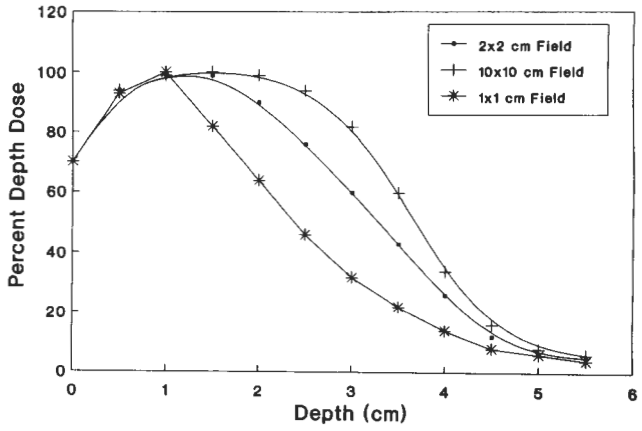


Figure 14-11. Percent depth dose for a 10-MeV electron beam. A 10 × 10-cm cone was used and blocked to a 2 × 2 and 1 × 1-cm field. All parameters except field size were held constant.

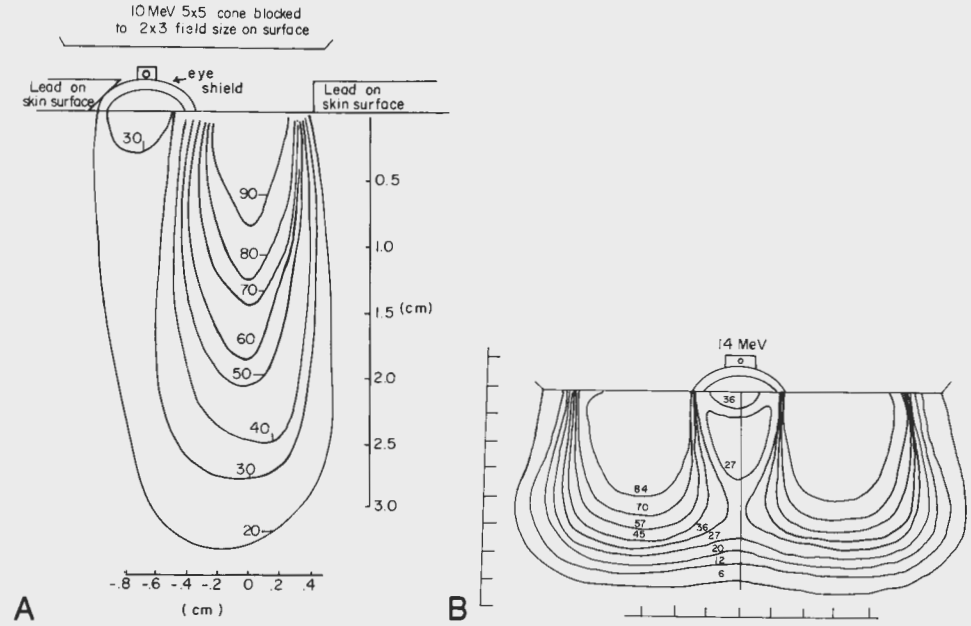


Figure 14-12. (*A*) Isodose distribution for a 2 × 3-cm 10-MeV electron-beam portal with eye shield (eg, for treatment of a lower eyelid lesion). Energies of approximately 10 MeV and higher can penetrate the shield and give substantial doses to the eye. For the case shown, a 5000-cGy tumor dose would deliver 1000 to 1500 cGy to parts of the shielded eye. (*B*) A 14-MeV electron-beam portal; 10 × 10-cm cone blocked to 7 cm diameter, 6 cm above surface. Eye shield on central axis. The combined effect of scatter plus beam penetration of the shield results in a high dose to the entire eye. In certain clinical situations this might be acceptable.

by using a common junction line. The general rule is to use a common match line between photon and electron fields and to treat the line with *both* the photon and the electron beam.

It is important to ensure that the treatment-planning system properly predicts the electron-beam isodose distribution for the specific treatment parameters used. For example, the dose distribution for an electron field blocked on the surface as opposed to one blocked 6 cm from the surface should be properly predicted by the electron-beam algorithm (Fig. 14-10). If the algorithm cannot predict such changes in dose distribution, the clinical parameters routinely used should be measured and modeled individually. Historically, skin cancer has been treated with orthovoltage units. Many of these treatments are being carried out with electron beams. Several problems involved in this transition must be examined to avoid underdosing the lesion or overdosing a normal structure (eg, the eye). The output (cGy/min) for small electron fields (1- to 3-cm diameter) depends on beam energy and the position of the BSBs. With beam diameters in the range of 1 to 3 cm, significant shifts in the electron beam's central axis, depth–dose characteristics can be observed (Fig. 14-11). This presents two problems. The first is the correct prediction of the isodose distribution for the specific clinical setup. The second is the correct calibration of the beam. If a relative output measurement is made at the initial depth of D_{max}, an incorrect block factor is obtained. For example, assume that a 2-cm diameter, 10-MeV electron beam is to be used and that the closest depth–dose curve available is for a 5 × 5-cm field. The depth of D_{max} for the 5 × 5-cm field is 2 cm. For the 2 × 2-cm field, this depth relates to the 88% isodose. If the patient's cone calibration was taken at this depth and not adjusted for the shift in depth dose, the dose delivered to that field would exceed the prescribed dose by 100/88, or 14%. The problem of field uniformity is critical, and for small fields, acceptable flatness can be achieved only by placing the final collimation on the skin surface. Side scatter under lead shields is also a problem. Eye shields are particularly susceptible to this problem because of their small diameter. For low electron energies (5 to 8 MeV), the beam scatter under the shield can result in unexpected doses to the eye. Higher-energy beams can also penetrate standard-thickness eye shields (Fig. 14-12). To compound these problems, the relatively low surface dose (70% to 80%) of low-energy (5 to 8 MeV) electron beams must be taken into account. If gross tumor lies at the surface, bolus must be used, in which case the field size (to allow for constriction of the 90% isodose lines), the given dose, or the energy must be increased to achieve the desired tumor dose. Orthovoltage energies remain the technique of choice in many clinics for skin cancers whenever clinically suitable.

COMPARISON OF PARALLEL OPPOSED PORTAL TECHNIQUES

The maximum dose and target tumor depth for a single portal occur at the same point only for relatively superficial lesions. An optimal treatment plan, one with a maximum tumor dose and a minimum dose to normal tissues, is usually achieved by a multiple portal arrangement. The most common arrangement in the irradiation of head and neck cancer involves parallel opposed lateral portals. Varying amounts of normal tissue are treated to doses as high as or higher than the prescribed tumor dose. With modern-day equipment, *the dose to tissues outside the tumor volume should seldom be more than 5% above the prescribed tumor dose;* treatment plans for complicated sinus lesions may deliver doses to normal tissue 10% to 12% greater than the tumor dose.

The ability to localize and create a homogeneous tumor dose is optimized by the choice of the correct beam energy and beam weight. Beams of ^{60}Co, 6-MV x-rays, and 17-MV x-rays for parallel opposed fields that are 5, 10, and 15 cm apart are compared in Figure 14-13. When the separation is increased from 5 to 15 cm, several interesting phenomena occur. First, at the small separations, the extensive buildup region of the higher-energy photon beam causes reduced doses near the skin surfaces. If desired, a greater uniformity across the separation is

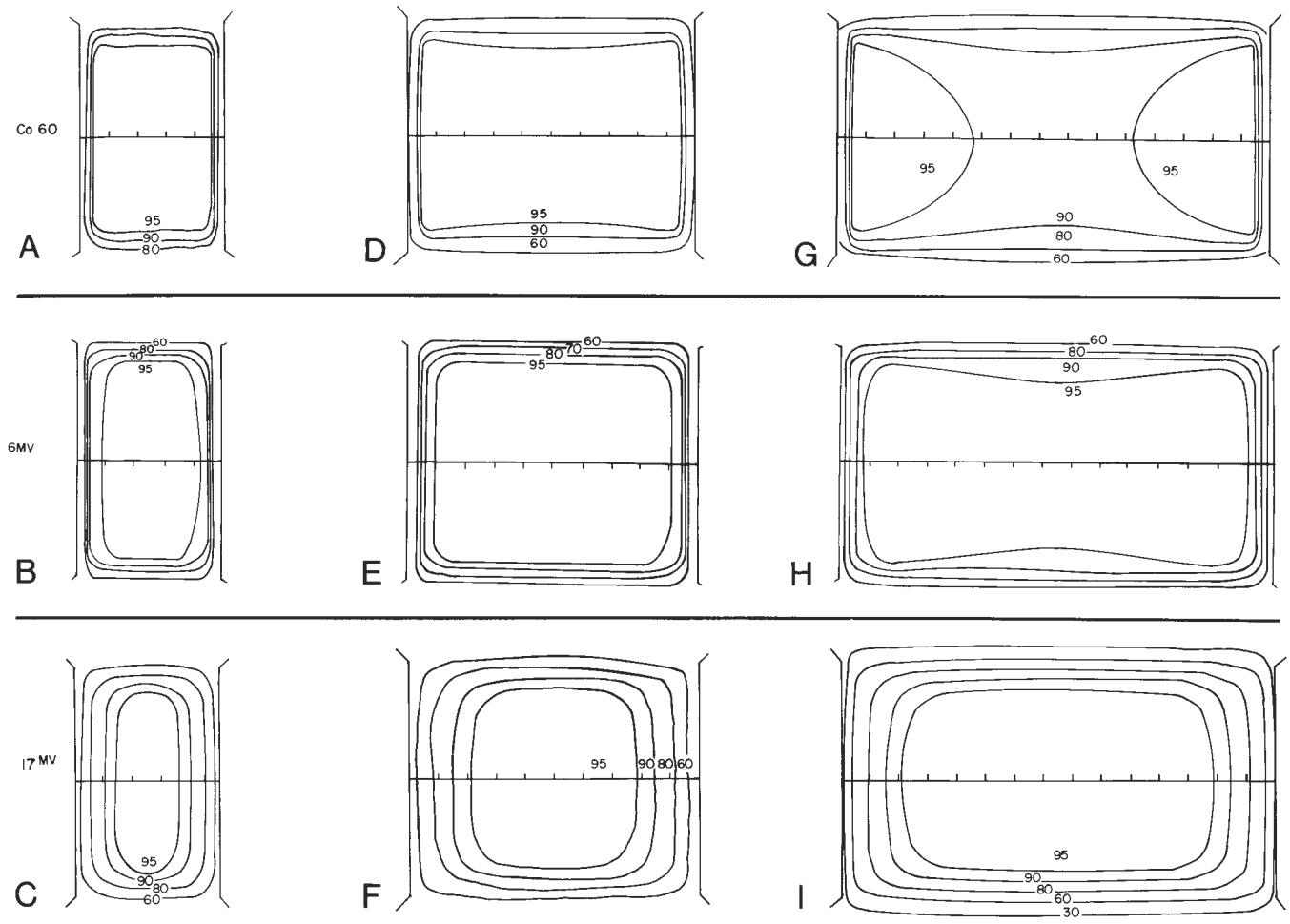


Figure 14-13. Comparison of the isodose distributions for ^{60}Co, 6-MV x-rays, and 17-MV x-rays for parallel opposed equally weighted 8 × 8-cm portals. ^{60}Co: SSD = 80 cm; 6 MV and 17 MV: TSD = 100 cm. (*A* through *C*) 5-cm separation. (*D* through *F*) 10-cm separation. (*G* through *I*) 15-cm separation.

achieved with the ^{60}Co. When a 15-cm separation is reached, however, the lack of dose at depth for ^{60}Co beams begins to create an area of low dose at mid-depth separations. At this point, the depth dose from the higher energy photon beams may offer a substantial advantage in certain clinical situations and a disadvantage in others.

A popular misconception holds that the falloff in dose near the edge of the portal is much greater with ^{60}Co than with linear accelerators; examination of the isodose distributions shows a small difference for the first 1 to 2 cm inside the geometric edge of the portals. The major advantage of higher-energy photons is the increased percentage depth dose and, in some instances, the decrease in the skin and subcutaneous dose. The edges of the portal are usually aimed at subclinical disease so that a slightly reduced dose is acceptable, if not desirable. When gross disease occurs near the edge of the portal (eg, carcinoma of the posterior pharyngeal wall), however, there are advantages to beams with less falloff near the beam edge.

COMPARISON OF TECHNIQUES FOR LATERALIZED LESIONS

A frequent situation in head and neck radiation therapy is a well-lateralized lesion to be managed mainly by external-beam irradiation. The following examples (Figs. 14-14 through 14-18) compare possible techniques for a carcinoma of the retromolar trigone/anterior tonsillar pillar.

A single ipsilateral ^{60}Co field enters the tumor region at the 93% isodose level and exits at the 80% isodose level, a gradient of 13% (see Fig. 14-14). The normal tissue at 5-mm depth receives a dose 20% greater than the minimum tumor dose. If a set of equally weighted, parallel opposed lateral ^{60}Co fields is used, the gradient across the region is 5% (90% to 95%; see Fig. 14-15*A*). The maximum dose to normal tissue is only 10% greater than the minimum tumor dose, but a much larger volume of normal tissue is exposed to a high dose. If the portals are weighted 2:1, there is still a 5% gradient across the tumor (see Fig. 14-15*B*). The maximum dose is 10% greater

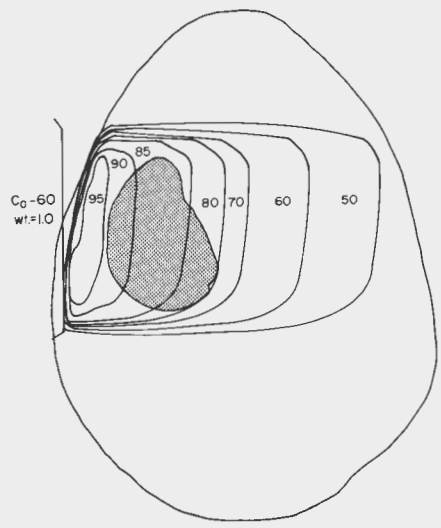


Figure 14-14. Single ^{60}Co field, 7 × 7 cm, SSD = 80 cm.

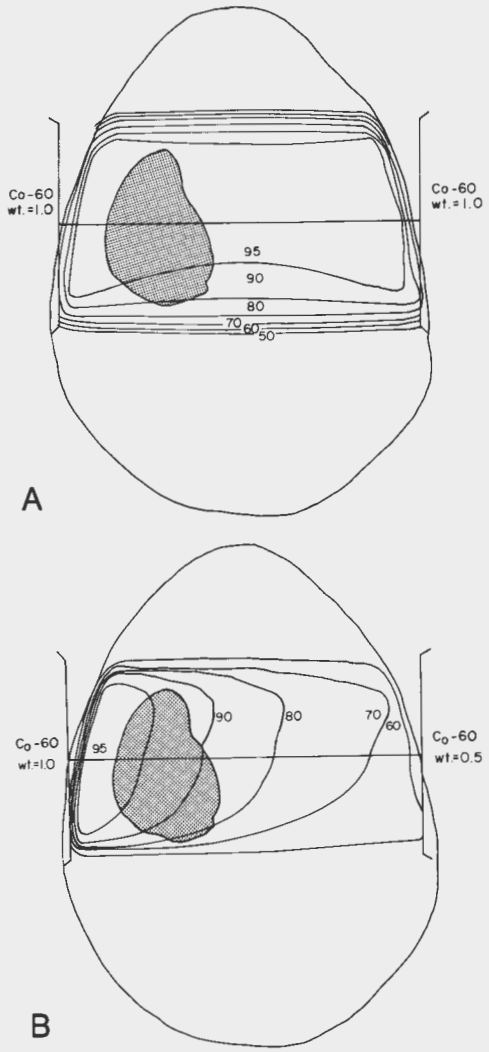


Figure 14-15. Cobalt-60 fields, parallel opposed, 7 × 7 cm, SSD = 80. (*A*) Weighted given dose 1.0 to 1.0. (*B*) Weighted given dose 1.0 to 0.5.

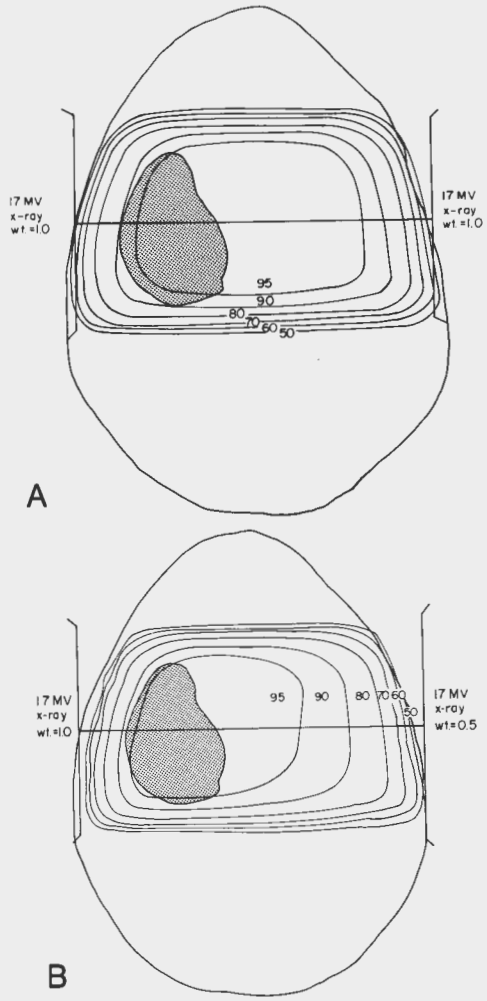


Figure 14-16. A 17-MV x-ray beam, field size 7 × 7 cm, SSD = 80. (*A*) Weighted given dose 1.0 to 1.0. (*B*) Weighted given dose 1.0 to 0.5.

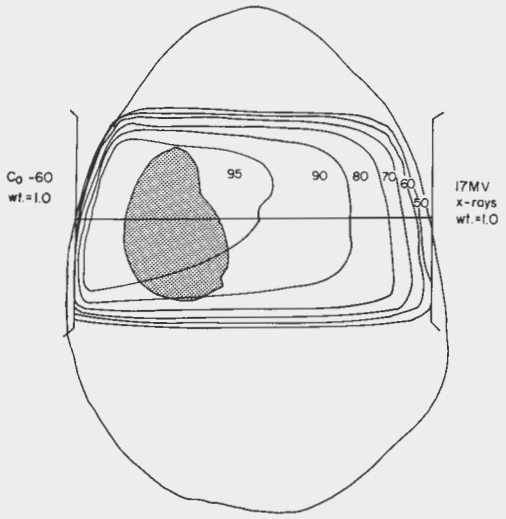


Figure 14-17. Cobalt-60 (SSD = 80 cm) and 17-MV x-rays (SSD = 100 cm), parallel opposed fields, field size 7 × 7 cm. Weighted given dose, ^{60}Co to 17-MV x-ray, is 1.0 to 1.0.

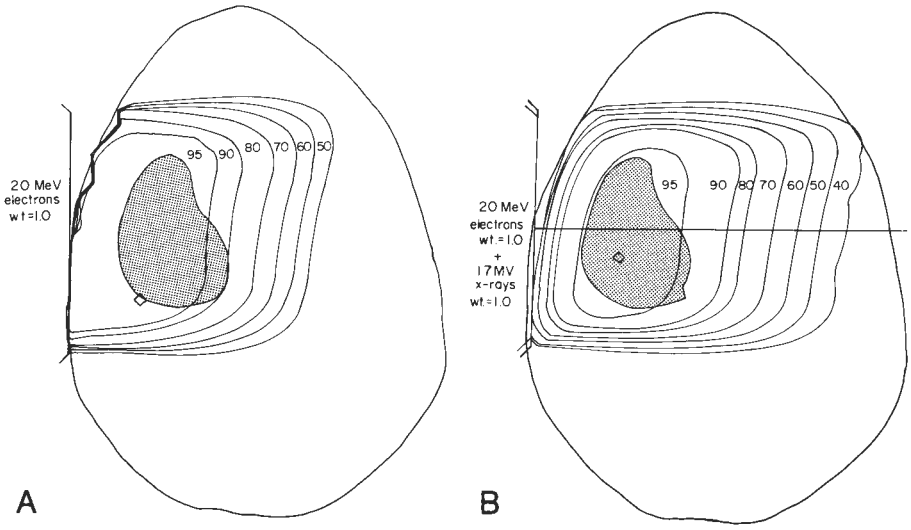


Figure 14-18. (*A*) 20-MeV electrons, field size 8.5 × 8.5 cm, SSD = 100 cm. (*B*) 20-MeV electrons, field size 8.5 × 8.5 cm, and 17-MV x-rays, field size 7 × 7 cm. SSD = 100 cm for both. Weighted given dose is 1.0 to 1.0. The addition of the 17-MV x-ray beam reduces the surface dose and gives a dose distribution that is affected less by bone.

only on the ipsilateral side, and the high-dose volume is reduced. There would still be sufficient dose to deliver 4500 to 5000 cGy to the contralateral lymph nodes. If the tissues extending to the right and left skin surfaces are at risk, the parallel opposed ^{60}Co fields are satisfactory. If the cervical lymph nodes are not clinically involved, however, a high-energy (6 to 17 MV) photon beam can adequately cover the region and reduce the volume of superficial normal tissue exposed and still deliver an acceptable dose (eg, 4500 cGy) for subclinical disease in the lymph nodes. At least 1 cm of skin and subcutaneous tissues overlies the lymph nodes at risk in the upper and midneck, and they would fall within the 70% to 95% depth dose (see Fig. 14-16). A combination of ^{60}Co and 17-MV x-rays can improve the distribution in certain situations (see Fig. 14-17). This combination may be used when there is a requirement for only 4500 to 5000 cGy to the contralateral upper-neck lymph nodes, 5000 to 5500 cGy to cover possible mucosal spread near the midline (7 cm), and 7000 cGy or more to the tonsillar area (3.5 cm) and ipsilateral neck.

A third or fourth portal may be added in certain clinical situations to further localize the high-dose volume to the area of interest (see Chap. 23; section on base of the tongue in Chap. 17; Chap. 22; and section on vocal cord carcinoma in Chap. 18).

A common technique for lateralized or superficial lesions is a combination of electron and photon beams, or only electrons (eg, parotid gland, early anterior tonsillar pillar or retromolar trigone, buccal mucosa, nasal vestibule, skin).

If a tumor volume extends 1 to 4.5 cm deep from the skin surface, a simple ipsilateral 20-MeV electron beam adequately covers the region (eg, carcinoma of the retromolar trigone and anterior tonsillar pillar). This volume would include the ipsilateral lymph nodes at risk in the upper neck. Because of the rapid falloff of the electron beam, the dose 3 to 4 cm past the tumor volume is usually less than 50% of the tumor dose. The use of only electrons in this situation has two disadvantages—high skin dose and differential absorption by the mandible. The use of a single high-energy electron field can often result in a dose at 5 mm of 95% to 100%. Although this dose may be acceptable, it may be advantageous to lower it at the price of a slight increase in the dose at depths beyond the tumor.

The use of a single 20-MeV electron beam (uncorrected for bone absorption) to treat a bulky retromolar trigone or anterior tonsillar pillar lesion is shown in Figure 14-18*A*. The surface dose is 90% and the dose at 5 mm is 95%, whereas the dose 3 cm past the tumor volume is at the 50% isodose line. The addition of a 17-MV x-ray beam would result in the distribution shown in Figure 14-18*B*. The dose to the subcutaneous tissues at 5 mm is decreased to 50%, the tumor is confined to a 6% gradient, and the tissues 3 cm beyond the tumor volume are at the 70% depth–dose line. The overall effect is the reduction of the high dose to the subcutaneous tissues and an elevation of dose to tissues beyond the tumor, but not beyond acceptable levels. One critical organ in this example would be the contralateral parotid; if the dose is limited to 3000 cGy, there is usually an approximate 50% recovery of saliva on one side. An intraoral shield further reduces the contralateral dose. The addition of a high-energy photon beam also decreases the effect of inhomogeneities such as the mandible.

The combination of photons and electrons offers a simple alternative to ipsilateral angled wedge portals. Advantages of the combined beam compared with angled wedge portals include the ability to tailor the entrance beam to fit the tumor volume, the ease of reduction of portals, and the relatively simple inclusion of contiguous lymph node groups.

The mixture of the electrons and photons is usually straightforward. The combined depth dose generally moves the 90% depth dose less than 1 cm compared with electrons alone. When the beams are weighted equally, the choice of electron beam is similar to that for the single beam case. For maximum skin-sparing, the highest available photon beam is usually the best choice; however, if the dose at the surface must be relatively high (eg, carcinoma of the skin or postoperative radiation therapy for parotid neoplasms), ^{60}Co or 4-MV x-rays yield a better distribution. More than two beam types may sometimes be used to develop the best distribution.

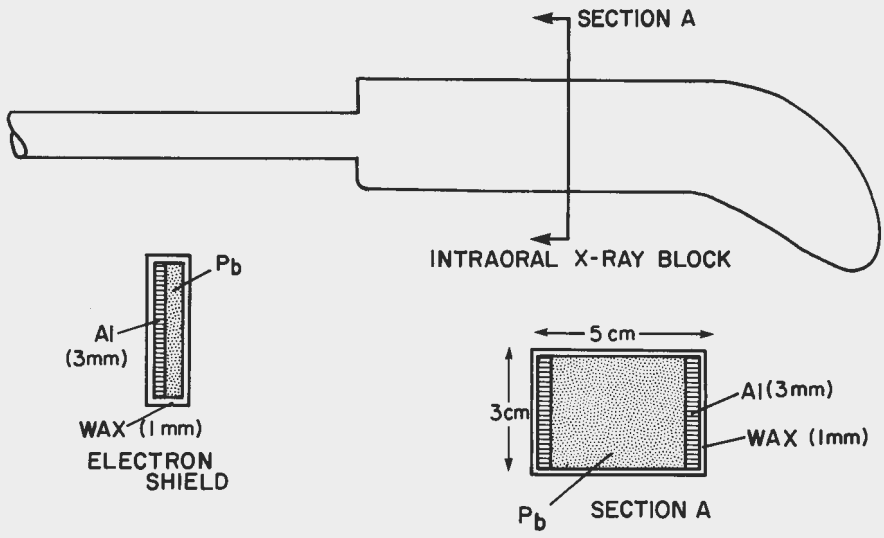


Figure 14-19. Intraoral block for high-energy photon and electron-beam treatment. The lead shield is covered with aluminum and wax to absorb extensive backscatter. Thin electron shields are coated with aluminum and wax for use behind a lip or ear.

COMPENSATION FOR SURFACE CONTOURS

Irregular surface contours can be compensated by wedges or full, individually tailored compensators.[3] One of the technical difficulties is the proper alignment of the compensating device with the surface. However, a small misalignment usually does not result in large inaccuracies. An exception to this rule would be the four-field box technique for treatment of the cervical esophagus (see Chap. 21). There is a sharp change in diameter of the lateral fields, and a small misplacement of the compensator in either direction would result in an incorrect dose. To eliminate this possible error, a large wax surface compensator is used. The disadvantage of this technique is the loss of skin sparing, although this has not presented a serious clinical problem in the esophagus technique; this disadvantage is offset by the simplicity of compensator fabrication and the ease of daily treatment alignment.

INTRAORAL BLOCKING

A beam absorber can sometimes be inserted intraorally for both photon and electron therapy to reduce transit irradiation. For example, if a simple orthovoltage treatment is to be given to the lower lip, a lead shield can easily be fabricated to spare the underlying structures from the transmitted radiation. When such shields are used, a thin (1 to 2 mm) coat of wax is necessary to protect the inner lip from backscatter dose from the lead shield (see section on the lip in Chap. 16).

If higher-energy photon or electron beams are used to treat lateralized lesions in the oral cavity or oropharynx, an intraoral shield can be of use. This shield is usually several centimeters thick (Fig. 14-19). Because of the variation from patient to patient, a variety of shapes and sizes are useful. Care must be given to the fabrication of the intraoral shield to avoid excessive backscatter from the lead to the adjacent tissue. The increase in dose due to backscatter is well documented for both gamma and electron radiation. Backscatter measurements from a lead surface for 250-kVp through 17-MV photons and 5- through 20-MeV electrons are presented in Table 14-1.

For 250-kV photons and ^{60}Co, a thin coat of wax over the lead is sufficient to absorb all of the backscattered beam. When the photon energy is increased to 8- or 17-MV x-rays, or when 5- to 20-MeV electrons are used, however, a composite of 3 mm aluminum and 1 mm wax is required to effectively reduce the backscatter dose from these beams. All intraoral blocks are fabricated with aluminum and beeswax, which eliminates the potential error of using the wrong shield for the high-energy photon beams (see Fig. 16-72 for an example).

TABLE 14-1. Backscatter Measurements: Percent Increase Above Homogeneous Dose

Millimeters of Absorber Placed Over 3 cm of Lead	250 kVp*	^{60}Co*	8 MV*	17 MV*	5 MeV†	10 MeV†	20 MeV†
None	170	110	100	90	70	50	30
0.4 mm wax	0	50	60	70	No data	No data	No data
3.0 mm wax	0	0	20	30	No data	No data	No data
3.0 mm Al	No data	No data	20	30	10	10	20
3.0 mm Al + 1 mm wax	0	0	10	10	10	10	20

* Relative ionization.

† Relative TLD response (Hershaw TLD-100 chips), measurements at a depth equal to D_{max}.

INTERSTITIAL THERAPY

Interstitial therapy has undergone significant improvements in technique and dosimetry over the past few decades. As recently as the late 1960s, it was common to implant head and neck lesions free-hand with radium needles and compute the dose distribution with the Paterson-Parker or Quimby systems. This procedure did not allow a precise dose–volume computation. The Paterson-Parker tables were constructed to give an *effective minimum dose*, a dose 10% above the absolute minimum for a plane or volume. For planar implants, the point of specification was a plane 5 mm from the implant, whereas for multiple planes, it was the midpoint between planes. For volume implants, the point of dose specification was 2 to 3 mm outside the circumference of the implant with a dose variation of 10% to 25% across the volume. These calculations did not identify regions of dose inhomogeneity. The adoption of computer-based treatment planning systems in the 1960s allowed reconstruction of implants from orthogonal or stereoshift roentgenograms for routine clinical use. Dose computations in planes of interest allowed the therapist to consider the dose inhomogeneity in prescribing the duration of the implant.

The choice of isotopes for implantation has also expanded from radium-226 (^{226}Ra) and radon-222 to include cesium-137 (^{137}Cs), iridium-192 (^{192}Ir), iodine-125 (^{125}I), and gold-198 (^{198}Au; Table 14-2).

Cesium-137

Cesium-137 needles are commonly used as a replacement for radium and are usually calibrated in milligrams of radium equivalent. The photon spectrum for ^{137}Cs is different from that for radium, but the dose distribution near the sources is similar because of the more important effect of inverse square.

The half-life of ^{137}Cs (30 years) is long enough to be ignored during a single implant. The entire inventory, however, must be decayed at the rate of 2% per year. This decay is the only disadvantage of ^{137}Cs compared with ^{226}Ra. After 10 years, the dose rate from an interstitial implant is decreased by 20%. The biologic importance of dose rates is discussed in Chapter 12.

There is an advantage in radiation protection with ^{137}Cs. The problem of leakage as experienced with radium is reduced because ^{137}Cs can be effectively shielded with lesser thicknesses of lead or concrete.

Needles containing ^{137}Cs are of a smaller diameter than radium needles and can be obtained in an afterloading form; however, it may be difficult to afterload the rigid needles in certain clinical situations. Although the use of ^{137}Cs addresses some of the problems of radiation protection, the problems of source lengths (less than 6 cm active length) and inability to implant along curved lines remain.

Iridium-192

Iridium-192 is usually obtained as seeds loaded into a flexible nylon sheath or thin, flexible wire sources used in the shape of a hairpin. The strength and interspacing of the sources can be altered to suit individual case requirements. For example, if an implant requires linear sources spanning 6 to 8 cm, the use of ^{192}Ir allows one source to span this length instead of using two cesium or radium sources in tandem.

TABLE 14-2. Commonly Used Isotopes

Source	Half-Life	HVL (Pb)	Source Type	Type of Loading	Inventory	Sterilization	Dosimetry
^{226}Ra	1629 years	7.4 cm	Needles 0.51–6.0 cm active length	(See Chap. 16). Afterloading not generally available; may be preloaded	Usually purchased	Generally not sterilized	Relatively simple due to rigid source lines
^{137}Cs	30 years	5.3 cm	Needles 1–6 cm active length	Afterloading possible	Purchased or leased	Afterloading sheaths can be autoclaved	Same as radium
^{192}Ir	72 days	0.3 cm	Seeds or wire	Routine afterloading	Usually ordered for each case	Nylon sheaths must be gas sterilized and allowed to vent for 24 to 48 h	May be difficult when definable planes do not exist
^{198}Au	2.7 days	0.3 cm	Seeds	Individual seed usually loaded into preloaded cartridges for use with implant gun	Ordered for each case	Generally not sterilized	Generally single plane, relatively simple
^{125}I	60.2 days	0.025 mm	Seeds	Individual seed and preloaded	Ordered for each case	Flash sterilized before implantation	Volume implants have problems similar to iridium-192

HVL = half-value layer; Pb = lead.

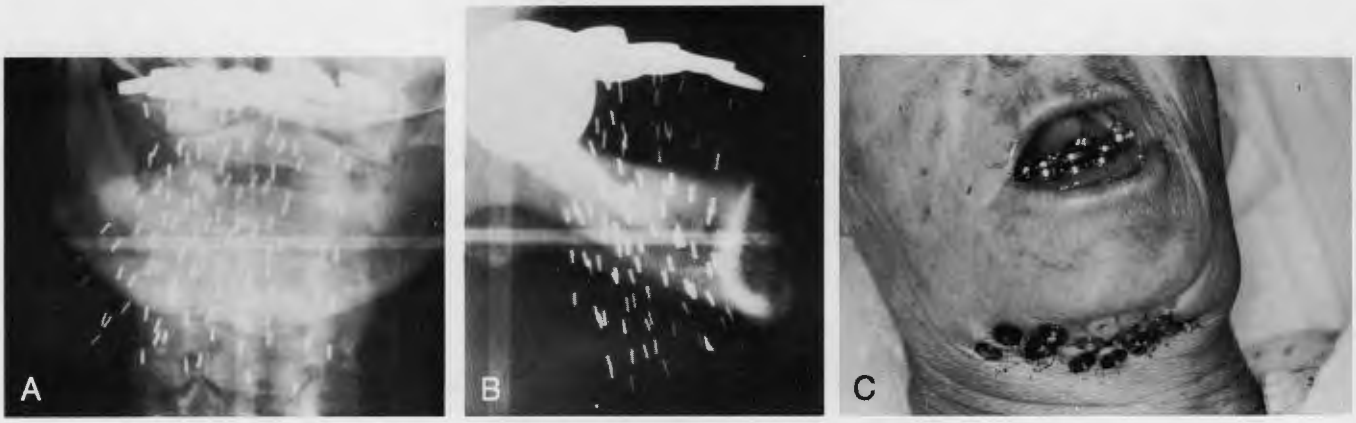


Figure 14-20. (*A*) Anteroposterior roentgenogram of an ^{192}I implant in the floor of the mouth. The ability to use long, flexible sources is of substantial aid in implantation of large lesions. (*B*) Lateral roentgenogram. (*C*) For implants of the floor of the mouth, it is advantageous to shield the structures superior to the implant by capping the nylon after loading tubes with gold or stainless-steel shields. Either crimping the ends of the source with metal buttons or melting the ends against nylon buttons secures the source in the nylon tubes. The small diameter and flexibility of the source result in little edema compared with a radium or cesium implant of the same volume.

The short half-life of ^{192}Ir (72 days) is both an advantage and a disadvantage. It usually requires the iridium to be ordered individually for each case, 4 to 5 working days before the scheduled implant. However, this also allows the specification of source strength to be adjusted for each implant.

There are several techniques for implanting ^{192}Ir. They all have the common advantage of afterloading. This is a substantial advantage in large implants, for which the dose rate at 1 m from the patient is often in excess of 100 mRem/h. This high dose rate can pose a substantial protection problem in the postoperative recovery area. The ability to afterload the implant in the patient's room significantly reduces the problem of exposure of personnel; however, the high dose rates often require shielding of the hospital room.

Although the flexibility of iridium sources enables complex implants to be performed, it also makes dosimetry substantially more complex. The location of 100 to 200 iridium seeds on orthogonal or stereoshift roentgenograms is more difficult than the entry of linear sources. The matching of the dosimetry with the patient's anatomy is also difficult because of the absence of the plane that would have been created by rigid linear sources (Fig. 14-20).

Seed Implants

For areas where temporary implants are difficult to use, such as the soft palate and posterior pharyngeal wall, permanent seed implants have been used. They have also been used for molds and for palliative treatment of lymph node metastases. The isotopes available are ^{198}Au and, more recently, ^{125}I. The half life of ^{198}Au (2.7 days) is substantially shorter than that of ^{125}I (60 days). The clinical effect of this difference is not known. Both types of seeds have the advantage of preloading into a cartridge.

TREATMENT PLANNING FOR IMPLANTS

The preplanning of implants is particularly advantageous if customized preloaded devices are used or if isotope strength must be determined, such as for ^{192}Ir and ^{198}Au implants. The best dose estimate is obtained by mocking up the implant and computing the dose distribution.

The reconstruction of the actual implant from either stereoshift or orthogonal radiographs, although relatively simple for planar implants, is complex for volume implants. Seed identification becomes difficult, and error checking is a necessary part of the reconstruction algorithm. When a large number of sources are to be matched, it is tempting to use stereo views and small shift distances (ie, 100-cm tube-to-implant distance ±15-cm shifts); however, these small shifts may result in large errors in source placement.[2] To minimize such errors, a shift distance should be used that is two thirds the tube-to-implant distance.

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15

THE UNKNOWN PRIMARY

RODNEY R. MILLION, NICHOLAS J. CASSISI, AND ANTHONY A. MANCUSO

"The Unknown Primary" sounds like the title for a whodunit rather than a medical treatise. In fact, the search for the site of origin of metastatic neck disease does resemble detective work, and the riddle is not always solved. Failure to detect the primary tumor site in patients presenting with metastatic cancer in neck lymph nodes represents 2% to 3% of the total head and neck cancer cases.[7]

Spontaneous remission of the primary site is assumed to have occurred in a portion of squamous cell carcinoma cases, because successful surgical treatment of the neck and long-term follow-up may never reveal the site of origin. Spontaneous remission is also occasionally reported for the primary site in breast cancer, testicular tumors, malignant melanoma, neuroblastoma, and others. At one time, many of these unknown primary neck masses were thought to arise from branchial cleft epithelial remnants in the soft tissue of the lateral neck, but current opinion argues against this site of origin except in a few instances.[6,9]

When neck dissection only is the initial treatment, 27% develop a primary lesion; 6% develop a mucosal primary in the radiation therapy group, and 15% develop a mucosal primary in the combined surgery and radiation therapy group.[12]

PATHOLOGY

The histology of the neck mass reflects the possible site of origin, but all too often the biopsy reveals a poorly differentiated neoplasm; lymphoma should be excluded by proper studies.

Adenocarcinoma almost always originates from below the clavicles, but if it occurs in the upper neck, a search for a major or minor salivary gland tumor, thyroid cancer,[8] or the rare parathyroid cancer is required.

Metastatic melanoma may arise from skin or mucous membrane and may be difficult to diagnose in the absence of melanin with only the use of light microscopy and hematoxylin and eosin stains. Immunophenotyping with S-100 and HMB-45 antibodies generally provides a definite diagnosis.

Fishkin and Spiegelberg[1] reported two cases in which plasmacytoma was diagnosed in cervical lymph nodes 2 years before the discovery of the primary lesions in the epiglottis and nasopharynx; we have observed a similar case presenting in a supraclavicular lymph node with a primary site not discovered.

PATTERNS OF SPREAD

Patterns of Evolution of Primary Site

If only the metastatic neck masses are treated, the primary lesion may never appear or it may appear later over a wide time range. The incidence of the primary lesion becoming manifest depends on the initial treatment. The overall eventual appearance of a primary lesion in the head and neck region is reported in 11% to 54% of patients.[12] These estimates are low because many patients die of regional persistence, distant metastasis, or intercurrent disease without a sufficient interval of observation. Appearance of a mucosal lesion, especially after 3 years, may actually represent a new and unrelated primary lesion.

Harper and associates reviewed 69 patients with unknown primary lesions managed by elective mucosal irradiation.[3] The actuarial risk of a subsequent mucosal lesion was compared with the risk for a series of 393 patients irradiated for known primary carcinomas of the supraglottic larynx, tonsil, and hypopharynx. The actuarial rate of subsequent appearance of mucosal primaries was similar in the two groups (Fig. 15-1). The unknown primary group included two soft palate cancers appearing 10 years after radiation therapy and one nasopharynx cancer appearing 11 years after radiation therapy. Nearly all reports show that elective mucosal irradiation reduces the risk of metachronous primary lesions compared with neck surgery only.

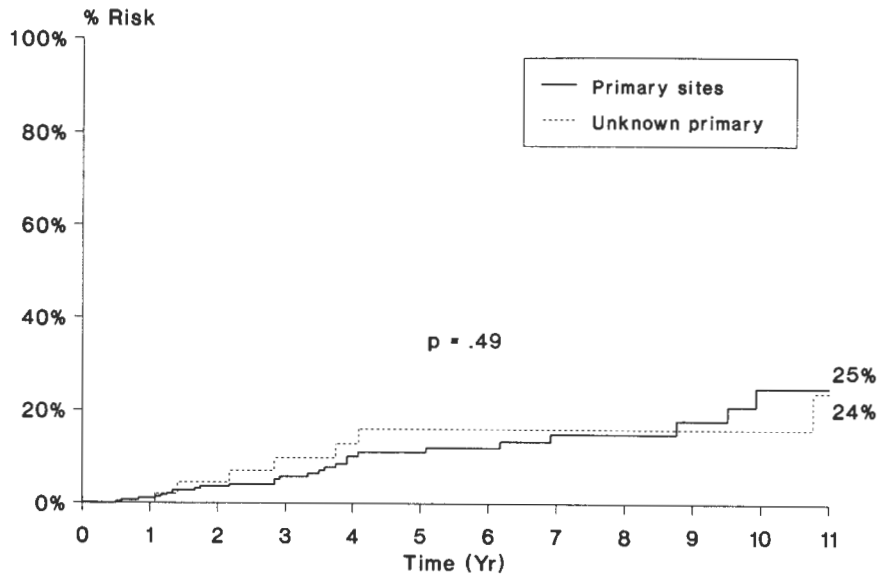


Figure 15-1. Incidence of mucosal site failure or second head and neck primary lesions after mucosal radiotherapy for unknown head and neck primary (*dashed line*) compared with incidence of metachronous second primary head and neck cancer after radiotherapy for squamous cell carcinoma of the tonsillar area, supraglottic larynx, pyriform sinus, and pharyngeal wall (*solid line*). (Harper CS, Mendenhall WM, Parsons JT, Stringer SP, Cassisi NJ, Million RR. Cancer in neck nodes with unknown primary site: role of mucosal radiotherapy. Head Neck 1990;12:467)

Computed tomography (CT) and magnetic resonance imaging (MRI) have demonstrated squamous cell cancers in the nasopharynx, tonsil, tongue base, hypopharynx, larynx, and esophagus when there was no evidence of mucosal disease even after careful panendoscopy. Waldeyer's ring is the area in which an occult lesion is almost always discovered by CT or MRI. Based on experience at several institutions, about 20% of otherwise undetectable primaries can be found or suggested by imaging when optimal technique and interpretation are available.

Patterns of Neck Involvement

The nodal distribution and neck stage for 69 patients presenting with squamous cell carcinoma in a neck mass and treated for cure are shown in Figure 15-2.

Harper and associates[3] reported a 42% incidence of a solitary mass (NX, N1, N2A) on presentation, and Wang and associates[12] reported a 48% incidence of a solitary mass on presentation. When multiple nodes are present, the location of the largest mass gives the same clue as a solitary mass to the probable location of a primary lesion.

Upper Neck

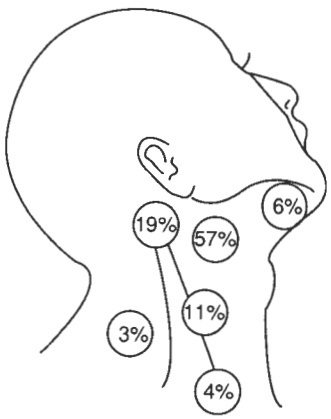
A solitary upper jugular chain mass is the most common situation, because virtually all head and neck cancers spread first to this area. Solitary upper neck lymph nodes rarely originate from cancers below the clavicles. If the mass is high in the upper neck, between the angle of the mandible and the tip of the mastoid, it suggests origin in the nasopharynx, oropharynx, or parotid, or occasionally a malignant melanoma or other skin cancer. If the mass is subdigastric in location, the oral cavity, larynx, and hypopharynx must also be included as likely sites. Non-Hodgkin's lymphoma may present as an upper-neck mass, but this is uncommonly seen in Hodgkin's disease. Bilateral upper neck nodes point to the nasopharynx, base of the tongue, soft palate, supraglottic larynx, pyriform sinus, and lymphoma as sites of origin.

A solitary submandibular mass suggests a site of origin in the oral cavity, lip, or nasal vestibule or a primary submandibular gland salivary tumor. CT helps distinguish a lymph node mass from the submandibular salivary gland.

A solitary submental node is rare.

Mid Neck

A solitary mid-neck mass favors the diagnosis of a primary tumor of the larynx, hypopharynx, or, less commonly, the thyroid or cervical esophagus or disease originating below the clavicle. Lymphoma should be considered.



NECK STAGE:	N1/X	N2A	N2B	N3A	N3B	TOTAL
No.	18	11	15	17	8	69
%	26%	16%	22%	25%	11%	

Figure 15-2. Site of presentation in unknown primary head and neck cancer treated for cure–69 cases. **Note**: University of Florida data; patients treated October 1964 to December 1986; analysis February 1989 by C. S. Harper, MBBS, DRACR.

Lower Neck and Supraclavicular Area

The solitary lower neck mass is most often metastatic from the chest or abdomen, but thyroid and cervical esophagus must be considered. Lymphomas commonly present in the lower neck. Rarely, a primary lesion of the head and neck presents in the low jugular or low posterior cervical region, having skipped the upper neck nodes.

Miscellaneous Sites

A solitary spinal accessory mass suggests a nasopharyngeal primary site. Squamous cell carcinoma occurring in the parotid area lymph nodes is almost always from a skin cancer and not a primary parotid neoplasm; a rare intraoral carcinoma may spread to the parotid area nodes.[10] The eustachian tube also drains to the parotid nodes; we have seen one case of a nasopharyngeal cancer presenting as a parotid mass.

Lymphoma and Leukemia

The distribution of the lymph nodes is a hint to the histology. Non-Hodgkin's lymphoma tends to involve the upper neck nodes, including the parotid, mastoid, submental, submandibular, and occipital lymph nodes. A careful search should be made for a mucosal primary lesion. Hodgkin's disease most often involves the lower neck nodes; a mucosal primary lesion is rare in Hodgkin's disease. Lymph nodes in patients with leukemia tend to be multiple, discrete, and bilateral.

CLINICAL PICTURE

The hallmark of the unknown primary syndrome is a painless, solitary neck mass that is usually discovered by the patient. About 15% have multiple ipsilateral masses, and the remaining 10% have bilateral neck lymph node metastases.[4] The mass is usually a minimum of 2 to 3 cm, but often is enormous. Because most benign neck masses also present as a solitary, painless mass, this history is of little help in the differential diagnosis. A history of a trial of antibiotics is common. The patient often reports that the mass "suddenly appeared" overnight. Mild discomfort in a carcinomatous lymph node usually indicates pockets of necrosis. Large, fixed, upper neck lymph nodes produce pain in the temporal or occipital area. Huge neck masses result in lymphatic obstruction, and the resulting lymphedema may bulge the lateral pharyngeal wall and tonsillar area. A localized area of erysipelas may appear proximal to the lymphatic blockage. Palsy of the facial, glossopharyngeal, vagus, spinal accessory, and hypoglossal nerves and the sympathetic nerve chain may occur.

Physical Examination

Routine head and neck examination must include inspection of the scalp, skin, and ear canal. A surgical or radiation scar may indicate prior treatment for a skin neoplasm. The clinical impression may be enhanced by the physical characteristics of the mass; soft, rubbery, matted nodes suggest lymphoma and leukemia, whereas rock-hard or fixed masses are more often carcinoma. Invasion of the skin may occur with any histology, including lymphomas.

DIAGNOSIS AND STAGING

A list of the seemingly endless possibilities in the differential diagnosis of a neck mass is provided below:

Benign

- Developmental
  - Inclusion cysts (sublingual and submandibular salivary glands)
  - Thyroglossal duct cysts
  - Congenital vascular malformations
  - Branchial cleft cysts
  - Cystic hygromas
  - Laryngocele
  - Teratomas
- Inflammatory
  - Benign reactive hyperplasia
  - Lymphadenitis (associated with upper respiratory tract infections, dental disease, cat-scratch fever, infectious mononucleosis, dermatitis, acquired immunodeficiency syndrome [AIDS], and others)
  - Infected sebaceous cyst
- Benign neoplasms
  - Hemangioma, lymphangioma
  - Thyroid nodules or goiter
  - Parathyroid adenomas
  - Lipoma
  - Fibroma
  - Neurofibroma
- Aneurysms

Malignant

- Metastatic carcinoma, sarcoma, or melanoma in lymph node
- Lymphoma or leukemia
- Carotid body tumor
- Glomus jugular tumor
- Soft tissue, bone, or cartilage sarcoma
- Primary major salivary gland tumor
- Malignant melanoma
- Adnexal carcinoma of the skin
- Thyroid cancer
- Parathyroid cancer
- Direct extension of a head and neck neoplasm into the neck
- Histiocytosis
- Plasmacytoma
- Carcinoid

The diagnosis by neck location for 207 patients who presented with cervical adenopathy and had a biopsy is shown in Table 15-1.[5] Only 10 (5%) were found to have squamous cell carcinoma without a demonstrable primary lesion. The most common diagnosis was a benign condition, except for supraclavicular lymph nodes. The age of the patient, the position of the mass, and the history quickly narrows the possibilities. The vast majority of 1- to 2-cm lymph nodes in children are inflammatory or reactive nodes. Midline masses are usually benign, with the exception of those in the thyroid gland.

A malignant supraclavicular mass usually represents lymphoma or metastatic disease from below the clavi-

TABLE 15-1. Diagnosis for 207 Patients Presenting With Cervical Lymphadenopathy

Location	Patients	Squamous Cell Carcinoma	Infroclavicular Metastasis	Lymphoma	Thyroid Carcinoma	Benign
Submental	15	0	0	13%	0	87%
Anterior cervical	25	12%	0	8%	20%	60%
Jugulodigastric	36	19%	14%	8%	8%	51%
Supraclavicular	49	0	39%	31%	2%	28%
Low postcervical	37	0	9%	39%	5%	47%

(Johnson JT, Newman RK. The anatomic location of neck metastasis from occult squamous cell carcinoma. Otolaryngol Head Neck Surg 1981;89:56)

cles, but, in the odd case, it may represent a regional metastasis from the cervical esophagus, a thyroid carcinoma, or even a primary sarcoma. If the histologic diagnosis is adenocarcinoma, the search for the primary lesion is directed toward those primary sites for which specific therapy may be recommended: the thyroid, breast; endometrium, prostate, and the rare adrenal cortex carcinoma. All of these tumors may respond to specific hormonal or drug therapy. The only lesion considered curable would be a carcinoma of the thyroid. It is usually fruitless and expensive to search for primary lesions in the lung, gastrointestinal tract, pancreas, and kidney, because there is no good specific treatment available for these malignancies. In any event, the primary lesion is found in less than 10% of patients in this situation.[11]

The remainder of this section deals with the patient who has disease predominantly in the middle and upper neck. The patient presenting with a neck mass is a common problem, and so are the errors surrounding the approach to diagnosis. An estimated 10% to 15% of patients with squamous cell carcinoma of the head and neck present because of a neck mass, and, for carcinoma of the nasopharynx, it represents the most common presenting complaint. Unless a clinical diagnosis of benign disease is certain, the diagnosis must be pursued according to the age of the patient, the location of the mass, and the remainder of the history and physical examination. A trial of antibiotics may seem harmless but may dangerously delay the diagnosis and treatment, and the patient may not return for follow-up if the mass "gets a little smaller." In fact, lymphomatous masses, both Hodgkin's and non-Hodgkin's, sometimes show a temporary decrease in size as part of their natural behavior. If the mass is probably a lymph node and lies in the upper two thirds of the neck, the initial work-up is a thorough search for a head and neck mucosal lesion.

In about 90% of cases, the primary lesion is found by physical examination. It has been our experience on several occasions to find the lesion after several previous negative examinations, including an examination with the patient under anesthesia. *Repeated examinations, especially examinations by several physicians, and contrast-enhanced CT or MRI scan are the key to finding the primary lesion* (Fig. 15-3). Examination under anesthesia with random biopsies uncommonly locates the primary lesion if the CT or MRI is normal. If the primary lesion is not found on physical examination, the next step is usually needle biopsy of the neck with frozen-section control if carcinoma is suspected. Several attempts may be necessary to get satisfactory tissue for diagnosis. If the needle biopsy is diagnostic for cancer, it directs the subsequent search for the primary lesion; a diagnosis of squamous cell carcinoma or adenocarcinoma is followed by CT or MRI to look for a possible primary site. If the biopsy is not definitive, CT or MRI may redirect the work-up (see Fig. 15-3*D*).

The CT or MRI examination should be done with contiguous 3- to 4-mm sections through the nasopharynx, oropharynx, larynx, hypopharynx, and entire neck. Technical factors should be optimized according to the principles presented in Chapter 4. MRI is used as a supplement for focused evaluation of areas suggestive but not definitely positive on CT or when CT is normal. MRI should be done as a first choice if iodinated contrast cannot be used for the CT study.

Panendoscopy and random or directed biopsies are the next steps after imaging and detect the primary lesion in about 20% of cases if a suspicious area is found on imaging. If the primary lesion remains undetected after the examination under anesthesia and if the results of the previous needle biopsies of the neck mass are negative or equivocal, open biopsy must be considered. The open biopsy of the neck mass is frequently done at the time of examination of the patient under anesthesia. The incision should be planned to facilitate either radical neck dissection or radiation therapy. Frozen section ensures that proper tissue is obtained. If lymphoma is suspected, the pathologist requires either a whole node or a generous portion of a large node for examination. This is especially true for Hodgkin's disease, and one of the largest accessible nodes should be excised, because smaller adjacent nodes are often not diagnostic (see Chap. 34).

Physicians unfamiliar with head and neck cancer frequently go directly to open biopsy of a neck mass after cursory or no examination of the mucous membranes. Although this approach may not reduce the chance of cure, it may markedly increase the morbidity associated with treatment and adds an unnecessary procedure (see Chap. 6). If it is not malpractice, it is certainly poor practice for a physician not to perform a thorough head and neck examination.

TREATMENT

This section deals only with those situations in which a primary focus is not found, the histologic diagnosis is squamous cell carcinoma, and the location of the lymph nodes favors a head and neck mucous membrane site of origin.

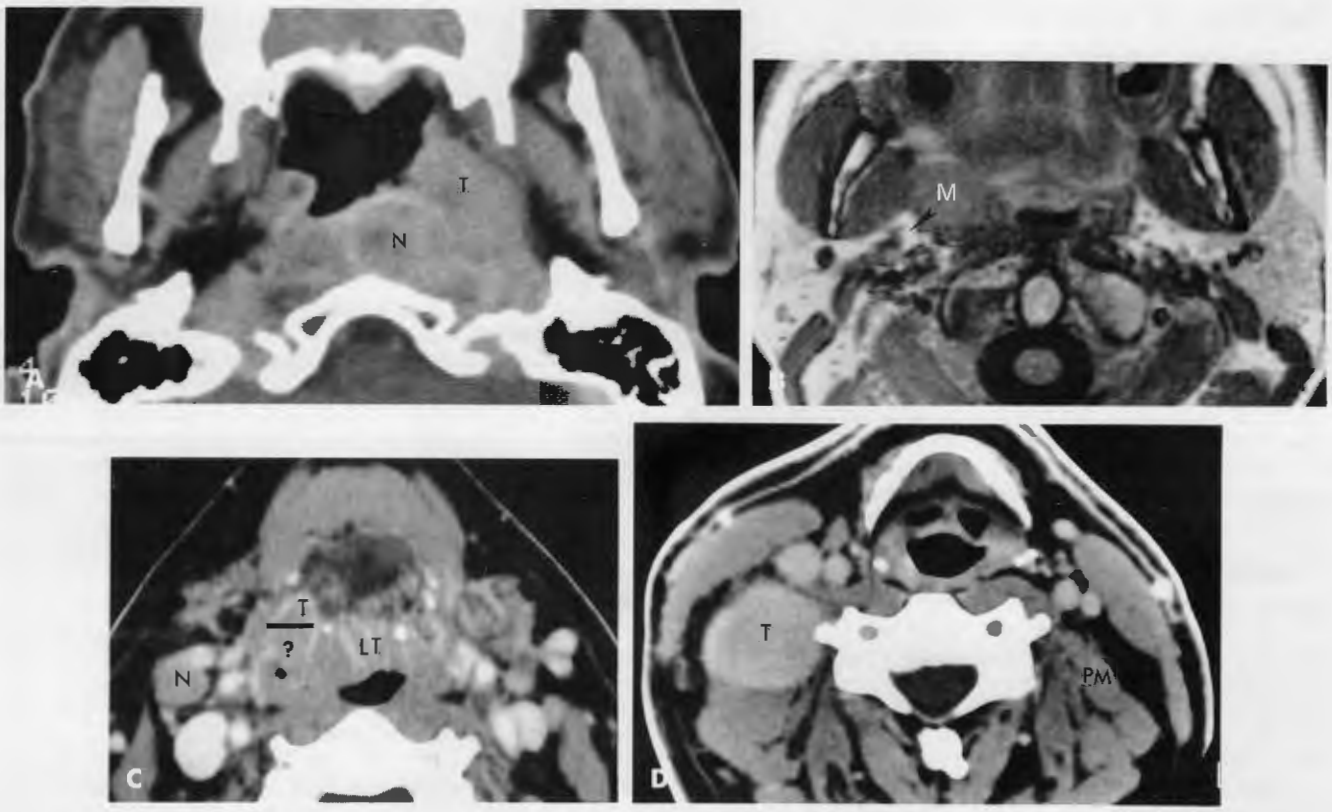


Figure 15-3. Four different patients presenting with an upper neck mass of uncertain etiology. Each patient had fine-needle aspiration biopsy of the *"node"* showing squamous cell carcinoma. The MRI and CT studies were done before panendoscopy in two patients and after negative panendoscopy in two others. (*A*) A 35-year-old man underwent panendoscopy with biopsies of normal-appearing nasopharynx, tonsil, tongue base, and hypophayrnx. After the negative panendoscopy, CT was done and showed an infiltrating tumor (T) of the lateral wall of the nasopharynx and the associated median retropharyngeal node (N). Repeat panendoscopy still revealed no evidence of mucosal abnormality, but a submucosal bulge was apparent. Deeper biopsies confirmed squamous cell carcinoma. (*B*) A 50-year-old patient who had a completely negative examination by multiple head and neck surgeons and radiation oncologists. MRI done before panendoscopy showed an approximately 1.5 × 1.5-cm infiltrating mass in the right faucial tonsil (M). The mass penetrated the superior constrictor muscle to infiltrate the parapharyngeal space (*arrowhead*); compare with the normal left side. At panendoscopy, no mucosal lesion was seen. Tonsillectomy revealed infiltrating squamous cell carcinoma. (*C*) The very top of an aspirated lymph node in this 55-year-old man can be seen on the right (N). Physical examination in the clinic, including palpation of the tongue base by numerous examiners, was negative. The CT revealed prominent lingual tonsillar tissue at the tongue base (LT). There was also a suspicious-appearing area in the lower right glossotonsillar sulcus (?); however, this could not be differentiated from variation in the amount of lingual tonsillar tissue. Just anterior to the questionably abnormal area, there was evidence of tissue (T) penetrating the tongue base. The horizontal black line separates the deeply infiltrating component, which penetrates the intrinsic muscles of the tongue base, from that portion of the mass that is indistinguishable from lingual tonsillar tissue. At panendoscopy, no mucosal lesion was seen. Deep biopsies in this area revealed invasive squamous cell carcinoma. (*D*) A 36-year-old man presented to our clinic after having had a negative panendoscopy at another institution after a neck biopsy interpreted as showing metastatic squamous cell carcinoma. CT of the upper aerodigestive tract and neck showed no evidence of a primary site. The tumor mass (T) actually does *not* lie in the normal lymph node-bearing areas of the neck. Careful evaluation of the image reveals that the tumor (T) actually arises in the paraspinous region deep to the prevertebral fascia. Compare the location of the mass to the normal paravertebral musculature (PM) on the opposite side. On the basis of its site of origin, it was suggested that this lesion more likely represented a sarcoma of either neural or muscle origin. The previous biopsy was reevaluated in light of these findings and considered suspicious for sarcoma. Repeat, open biopsy was performed and confirmed a neurogenic sarcoma.

Selection of Treatment Modality

It is clear that some patients can be cured by therapy confined to the neck, particularly the group with a solitary, well-differentiated subdigastric mass. However, should the primary lesion subsequently appear in the head and neck, many patients are unsuccessfully treated and the 3-year survival rate is reduced by one half.[4]

In the past, we have advocated elective irradiation of the mucosal sites at risk and both sides of the neck as the initial therapy for an unknown primary. The morbidity associated with treating this volume to 5500 to 6000 cGy over 6 to 7 weeks is significant and represents a certain amount of overkill. Our current thinking is that a reliable patient who has been examined by multiple examiners and had CT or MRI radiographic evaluation can be managed in selected cases by neck treatment only.

For example, if the patient has a solitary, well-differentiated, mobile lymph node diagnosed by needle biopsy, neck dissection alone may be sufficient, and the primary lesion can be treated if it appears.[4]

However, a high proportion of patients have an indication for radiation therapy based on the neck disease. Excisional or incisional biopsy of the neck before definitive treatment is an indication to use radiation therapy (see Chap. 6). Multiple positive lymph nodes and extracapsular extension are also indications for combined therapy. Therefore, relatively few patients are suitable for only neck surgery and observation. When radiation therapy is indicated for neck control, it is advisable to include the mucosal sites at risk. The mucosal sites to be electively irradiated vary according to the location and distribution of the lymph nodes but often include the nasopharynx, oropharynx, supraglottic larynx, hypopharynx, and both sides of the neck. An appropriate neck dissection is added, as outlined in Chapter 6. This approach represents a certain amount of overkill. It has the advantage of complete treatment at the first instance with a small risk of a primary lesion subsequently appearing and an excellent chance of neck control with combined therapy. The major disadvantage is the sequela of xerostomia after 5500 to 6000 cGy over 7 weeks.

The control rates for neck disease at the University of Florida according to the treatment plan are shown in Table 15-2.[3] If a single lymph node has been excised, radiation therapy alone is sufficient. N1 and N2A patients who have complete regression during radiation therapy are usually managed by radiation therapy alone; neck dissection is added for incomplete regression. Patients with more advanced disease or after incisional biopsy usually have a neck dissection 4 to 6 weeks after radiation therapy. It is a moot point whether to do the neck dissection before radiation therapy or afterward for mobile disease. However, for N3A disease or incisionally biopsied masses, we prefer to start with radiation therapy. Treatment of bilateral neck disease must be individualized (see Chap. 6).

TABLE 15-2. Hemineck Control by Stage (61 Hemenecks in 54 Patients)

Treatment	N1/NX	N2A	N2B	N3A
Radiotherapy alone	18/18	7/7	2/4	2/9
Radiotherapy plus neck dissection	2/2	5/5	7/8	4/8

(Harper CS, Mendenhall WM, Parsons JT, Stringer SP, Cassisi NJ, Million RR. Cancer in neck nodes with unknown primary site: role of mucosal radiotherapy. Head Neck 1990;12:468)

Low Neck Disease

Supraclavicular nodes usually represent metastasis from the chest, abdomen, or breast and, therefore, are usually an incurable situation.

If the patient is otherwise in excellent condition, an attempt should be made to control the supraclavicular disease, because a few patients live a long time before other disease becomes manifest; an occasional patient with either squamous cell carcinoma or adenocarcinoma is reported to live over 5 years with a primary focus never being observed. Neck dissection is considered but seldom recommended. Those patients who are pursuing a downhill course are either given a short course of palliative radiation therapy (eg, 1000 cGy twice, 1 week apart) or just observed.

Surgical Treatment

A discussion of neck dissection is provided in Chapter 6.

Irradiation Technique

Treatment planning depends on the location of the lymph nodes. Upper and midjugular lymph nodes indicate elective irradiation of the nasopharynx, oropharynx, supraglottic larynx, hypopharynx, and both sides of the neck to the level of the clavicles; the oral cavity is not included. If the lymph node is located very high in the neck (ie, junctional node or lateral retropharyngeal node), elective radiation therapy may be confined to the nasopharynx and oropharynx. If the lymph node is in the midjugular region, elective radiation therapy may be confined to the hypopharynx, supraglottic larynx, and oropharynx. A solitary submandibular lymph node is preferably treated by neck dissection and observation, because irradiation of the entire oral cavity plus the neck causes major morbidity. A preauricular lymph node (or nodes) containing squamous cell carcinoma almost always represents metastasis from a skin cancer and is treated by a combination of parotidectomy and radiation therapy or radiation therapy alone (see Chap. 25). Involved supraclavicular nodes are irradiated through a generous regional portal, which should include the adjacent apex of the axilla.

An analysis of the dose for control of subclinical disease at the unknown primary site for 39 patients shows a trend to fewer failures with increasing dose. The current policy is to plan 5500 cGy at 180 cGy per fraction and to add an extra 500 to 1000 cGy in three to five fractions to any suspected site. The dose for subclinical disease at the primary site needs further study and is complicated by the fact that patients develop second head and neck primary tumors that cannot be distinguished from a failure to eradicate the subclinical lesion. It is important to spare a midline strip of neck skin to avoid lymphedema. An individualized treatment plan for a patient with bilateral neck disease is shown in Figure 15-4.

The neck is usually thinner than the head, and this difference must be adjusted by compensators or portal reductions at appropriate times.

TABLE 15-3. Three-Year Absolute Survival, Free of Cancer

Stage	Surgery	Radiation Therapy	Combination Therapy
NX	31/39 (79%)	8/9 (89%)	3/3
N1	4/6 (67%)	1/3	1/3
N2	10/22 (45%)	3/4 (75%)	5/9 (56%)
N3	14/37 (38%)	13/36 (36%)	4/13 (31%)
TOTAL	59/104* (57%)	25/52† (48%)	13/28† (46%)

* Salvage in eight patients by radiation therapy and six patients by surgery.
† Salvage in one patient by surgery.
Note: M. D. Anderson Hospital data; 184 patients treated July 1948 to June 1968.
(Jesse RH, Perez CA, Fletcher GH. Cervical lymph node metastasis: unknown primary cancer. Cancer 1973;31:858)

Management of Recurrence

If a head and neck primary lesion appears, management is individualized. If radiation therapy has not been used, the treatment decisions are governed by the anatomic site. If the new lesion is well outside a prior irradiation field and unsuitable for operation, irradiation may be considered. Limited recurrence in the neck may be suitable for radical retreatment by surgery, radiation therapy, or both. The appearance of a new lymph node in the neck requires repeat work-up for a primary site.

RESULTS OF TREATMENT

Fitzpatrick and Kotalik,[2] at Princess Margaret Hospital, Toronto, reported 233 patients presenting with an unknown primary lesion. The 5-year absolute survival rate was 18%. Among 68 patients with disease limited to the upper neck and midneck treated by irradiation to the neck and suspected primary sites and receiving a minimum dose of 4500 cGy over 4 weeks, the 5-year survival rate was 44%. The recurrence rate in the neck was 26% (18 of 68). The results were the same for squamous cell carcinoma and anaplastic carcinoma.

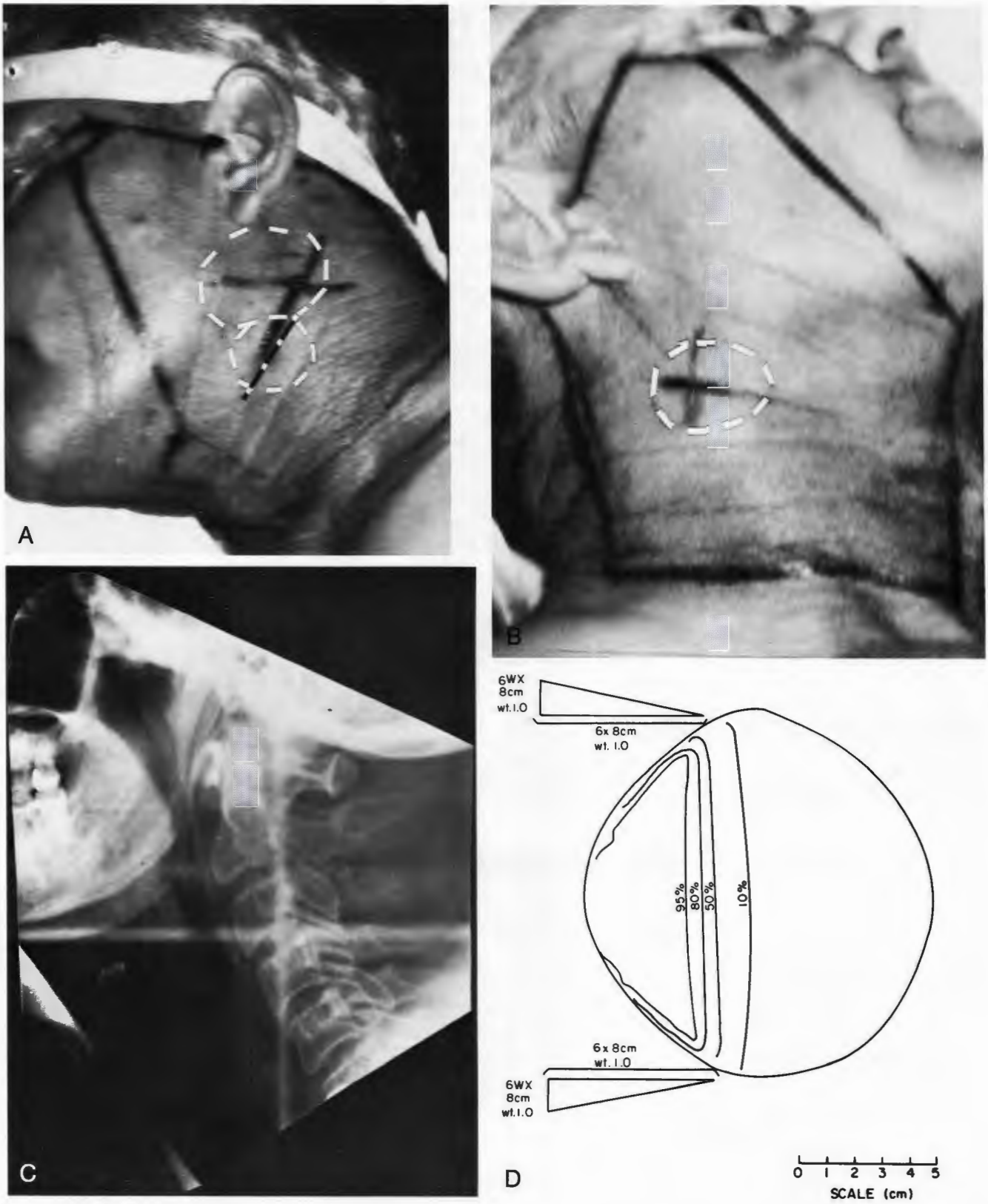
Jesse and coworkers[4] reported the M. D. Anderson Hospital experience for 184 patients with disease limited to neck nodes (excluding supraclavicular presentations). Treatment was individualized. The 3-year absolute survival rate was 53%, and the 5-year absolute survival rate was 43% of 151 patients. The survival by N stage and therapeutic category is shown in Table 15-3. The location of the primary lesion appearing after initial treatment is given in Table 15-4. No new mucosal lesions appeared within the irradiated areas. Although many of the patients were said to have had successful local treatment when the primary lesion finally appeared, the eventual result was poor owing to reseeding of the neck or to distant metastases. The 3-year survival rate was 31% for those in whom a primary focus appeared, compared with 58% for those who never developed a primary lesion.

Harper and associates[3] reviewed the University of Florida's 22-year experience for 69 patients with disease limited to neck nodes treated by radiation therapy alone (39 patients) or in combination with a neck dissection (30

TABLE 15-4. Location of Primary Lesion Appearing After Treatment

Location	Surgery	Radiation Therapy	Combination Therapy
Hypopharynx	6	1	1
Tonsil or faucial arch	4	0	1
Base of tongue, vallecula	4	0	0
Oral cavity, salivary glands	2	2	0
Nasopharynx	2	0	0
Maxillary antrum	0	0	1
Ayrepiglottic fold, epiglottis	1	0	1
Cervical esophagus	1	0	0
Thyroid	1	0	0
Total head and neck	21/104 (20%)*	3/52 (6%)†‡	4/28 (14%)‡
Below clavicle	5	3	1

* Primary lesion was controlled in 14 of 21 patients (8 by radiation therapy, 6 by surgery).
† Portals covered Waldeyer's ring in 45 of 52 patients.
‡ Primary lesion was controlled in 2 of 7 patients (by surgery).
(Jesse RH, Perez CA, Fletcher GH. Cervical lymph node metastasis: unknown primary cancer. Cancer 1973; 31:857)


A
B
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0 1 2 3 4 5
SCALE (cm)

Figure 15-4.

Figure 15-4. (*Continued*)

patients). Table 15-5 shows the mucosal site control related to mucosal sites treated, and Table 15-6 analyzes the mucosal control rate for three dose levels. Only two irradiated mucosal sites developed a primary lesion within 3 years. Control of disease in each side of neck according to the treatment plan is shown in Table 15-2; there were no failures in 47 clinically negative necks. The 5- and 10-year cause-specific survival rates were 66% and 62%, respectively. The 5- and 10-year absolute survival rates were 48% and 37%, respectively.

FOLLOW-UP POLICY

Follow-up includes a thorough head and neck examination at 4- to 8-week intervals for 2 to 3 years, every 3 to 4 months during the third year, and then every 6 months. Routine head and neck roentgenograms are not obtained unless indicated by the history. Approximately 10% of patients present with a head and neck primary lesion by 5 years and 20% by 10 years.

◄ **Figure 15-4.** A 51-year-old man presented with a 3-month history of a mass in the left neck. Multiple physical examinations and endoscopy with random biopsies of the nasopharynx, tonsillar fossae, base of the tongue, and pyriform sinuses revealed no mucosal primary lesion. An incisional biopsy was used to obtain tissue from the left neck node. Poorly differentiated carcinoma was reported. (*A*) The left neck contained a 5.3 × 3.0-cm high subdigastric node and an immediately subjacent 3 × 3-cm area of induration beneath the surgical scar (*dashed line*). No mucosal primary lesion was apparent. (*B*) There was a 4 × 5-cm right subdigastric node (*dashed line*). (*C*) A dose of 5000 cGy in 30 fractions was administered to the "unknown primary" treatment volume shown, including the nasopharynx, oropharynx, hypopharynx, and supraglottic larynx. The lower border includes the cricoid cartilage (C6). Note sparing of an anterior skin strip. The lower neck was treated with an anterior field (5000 cGy given dose in 25 fractions). (*D*) The dose to the right neck node was boosted by an additional 2000-cGy tumor dose specified at the 95% normalized isodose line, ^{60}Co, with a combination of anterior and posterior open and wedge fields. Weights (wt.) refer to the relative given doses to each of the four fields. The total tumor dose to the right neck node was 7000 cGy over 8 weeks. The medial field edge was placed 2 cm off the midline. For the posterior field, the patient was prone. The dose to the spinal cord from the tangential fields was less than 10% of the tumor dose. Because of the large volume of disease in the left neck, a radical neck dissection was performed 6 weeks after irradiation. No tumor was found in 38 nodes. (*E* and *F*) The patient was asymptomatic 6 years after treatment except for moderate xerostomia. He was using fluoride daily, and his teeth remained in good condition.

TABLE 15-5. Mucosal Site Control According to Area Treated* (65 Patients)

Mucosal Sites Irradiated	Exclusions†	Control With Initial Therapy	Surgical Salvage	Control After Salvage Therapy
Nasopharynx, oropharynx, hypopharynx	13	21/29 (72%)	2/3	23/29 (79%)
Nasopharynx, oropharynx	7	10/10	0/0	10/10
Oropharynx, hypopharynx	1	1/1	0/0	1/1
Oropharynx, oral cavity	2	2/2	0/0	2/2
TOTAL	23	34/42	2/3	36/42

* Excludes four patients (neck only treated).

† Died within 2 years of treatment with head and neck mucosa continuously disease-free.

(Harper CS, Mendenhall WM, Parsons JT, Stringer SP, Cassisi NJ, Million RR. Cancer in neck nodes with unknown primary site: role of mucosal radiotherapy. Head Neck 1990; 12:467)

COMPLICATIONS OF TREATMENT

The operative complications are essentially those associated with neck dissection (see Chap. 6).

The main radiation therapy complication is marked xerostomia. If the mucosal dose is 5500 cGy over 6 weeks to 6000 cGy over 7 weeks, there should be minimal persistent edema even though the entire supraglottic larynx and hypopharynx are included and a neck dissection is added. Bone exposure occurred in 2 of 69 patients reported by Harper and coworkers; one healed with conservative treatment, and one healed with hyperbaric oxygen therapy.[3]

TABLE 15-6. Radiotherapy Dose Versus Mucosal Site Control* (39 Patients)

Dose	Mucosal Control
4501–5000 cGy	13/16 (81%)
5001–5500 cGy	8/9 (89%)
5501–6000 cGy	13/14 (93%)

* Three patients excluded with out-of-field mucosal site failure; 23 patients excluded who died within 2 years of treatment with head and neck continuously disease-free; and four patients excluded who received treatment to neck alone.

(Harper CS, Mendenhall WM, Parsons JT, Stringer SP, Cassisi NJ, Million RR. Cancer in neck nodes with unknown primary site: role of mucosal radiotherapy. Head Neck 1990;12:463–469)

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16

ORAL CAVITY

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The oral cavity consists of the lip, floor of the mouth, oral tongue (the anterior two thirds of the tongue), buccal mucosa, upper and lower gingiva, hard palate, and retromolar trigone. The relative frequency of involvement by cancer for the various oral cavity sites is shown in Table 16-1.[35] Approximately 95% of carcinomas appear after the age of 40, and the average age is about 60. Acquired immunodeficiency syndrome (AIDS) and marijuana are associated with squamous cell carcinoma, particularly in the patient younger than 40. The use of tobacco in any form is associated with an increased risk of oral cancer. Smokeless tobacco (snuff) produces carcinomas of the buccal and gingival regions, coincident to the location of the quid, and is diagnosed most often in older, white women living in the Southern tobacco belt. Leukoplakia is found in association with oral carcinoma in approximately 15% of cases. The incidence of oral cavity cancers has shown little change in the past decade. The squamous mucosa of the oral cavity consists for the most part of a thick layer of squamous cells with rete pegs and a keratin layer. However, the floor of the mouth and the undersurface and lateral sides of the tongue have a thin mucosa with little surface keratin; coincidentally, these are the most frequent sites of cancer.

The American Joint Committee on Cancer (AJCC) staging system for primary tumors of the oral cavity is listed below.[3]

TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ
T1	Tumor 2 cm or less in greatest dimension
T2	Tumor more than 2 cm but not more than 4 cm in greatest diameter
T3	Tumor more than 4 cm in greatest dimension
T4 (lip)	Tumor invades adjacent structures (eg, through cortical bone, tongue, skin of neck)
T4 (oral cavity)	Tumor invades adjacent structures (eg, through cortical bone, into deep [extrinsic] muscle of tongue, maxillary sinus, skin)

For lymph node staging, see Chapter 6.
For stage grouping, see Figure 5-1.

LIP

The estimated number of new cases of lip cancer in the United States for 1993 was 3000 for men and 500 for women; the estimated risk of death was 100 per year.[9] The incidence of lip cancer seems to be decreasing. People with light-colored skin or with prolonged exposure to sunlight are most prone to develop lip carcinoma. Tobacco is a causative agent; the relationship to pipe smoking is undecided. Most cases appear after age 40, but about 10% occur before age 40 and a few before age 30. The disease is uncommon in blacks.

Anatomy

The lips are composed of the orbicularis muscle, with skin on the external surface and mucous membrane on the internal surface. The mucous membrane lining the inside of the lip is considered to be buccal mucosa and is rarely the site of malignant tumors. The dry lip is the transition from skin to mucous membrane. The muscle is covered by a thin layer of squamous epithelium that allows the underlying vasculature to show, thus giving the lips their reddish color. The blood supply is the labial artery, a branch of the facial artery. The motor nerves are branches of the facial nerve. The sensory nerve to the

TABLE 16-1. Distribution of Oral Cavity Cancer: 1717 Total Cases (MD Anderson Hospital)

Location	Percentage
Lip	44.9%
Oral tongue	16.5%
Floor of mouth	12.1%
Gingiva, lower	12.1%
Palate/upper gingiva	4.7%
Buccal mucosa	9.7%

(Data from MacComb WS, Fletcher GH, Healey JE Jr. Intra-oral cavity: In MacComb WS, Fletcher GH, eds. Cancer of the head and neck. Baltimore, Williams & Wilkins, 1967:89–151)

lower lip is the mental nerve, which is a branch of the inferior alveolar nerve. The commissure is supplied in part by the buccal branch of the mandibular nerve. The sensory nerve to the upper lip is the infraorbital branch of the maxillary nerve.

Pathology

The most common neoplasms are low-grade squamous cell carcinomas; about 5% are high grade. Basal cell carcinomas arise from the skin of the lip and may invade the vermilion, but do not arise from the vermilion. Verrucous carcinomas are rare. Benign lesions such as hemangiomas, fibromas, and cysts may involve the lips.

Severe dysplasia and leukoplakia are common problems on the lower lip and may precede the appearance of carcinoma by many years. Keratoacanthoma may occur and be mistaken for squamous cell carcinoma. Primary lesions arising from the moist mucosa of the lip are considered in the section on buccal mucosa in this chapter.

Patterns of Spread

Squamous cell carcinomas start on the vermilion of the lower lip, rarely on the upper lip. They usually appear on the sun-exposed vermilion between the commissures. The commissure is rarely the site of origin. Early lesions first invade adjacent skin and the orbicularis muscle.

Advanced lesions invade the adjacent commissures of the lip and buccal mucosa, the skin and wet mucosa of the lip, the adjacent mandible, and, eventually, the mental nerve. Perineural invasion occurred in 2% of the cases reported by Byers and coworkers[12] and was related to recurrent lesions, large tumor size, mandibular invasion, and poorly differentiated histology. Cancer may spread along the intraosseous portion of the inferior alveolar nerve and remain contained within the nerve without spread into the medullary cavity.[42] Lymphatic spread from the lower lip is first to the submental, submandibular, and subdigastric lymph nodes and rarely to a facial node. Lesions located near the midline may spread to either side. The lymphatic drainage of the upper lip is primarily to the neck lymph nodes, but occasionally the facial and parotid-area lymph nodes may be involved. A small, facial lymph node located near the mental foramen may become involved and be associated with nerve invasion. Lymph node involvement occurs in 5% to 10% on admission, but in 19% for lesions involving the commissure, because they are often larger and often associated with mucosal involvement. Of patients with a clinically negative neck, 5% to 10% subsequently develop lymph node metastasis.[36] The risk of lymphatic involvement is increased by depth of invasion, high-grade histology, large lesions, spread to involve the buccal mucosa, and invasion of the dermis; it is especially increased in patients with recurrent disease. Although lymph node metastases are relatively uncommon for early, low-grade lesions, they may be missed because they may not become evident for 3 or more years.

Clinical Picture

Asymptomatic red lesions are sometimes seen and resemble other red lesions of the oral cavity. Carcinoma of the lip may present as a slowly enlarging, exophytic lesion with an elevated border that is nontender unless it ulcerates and becomes infected. Occasionally, there is minor bleeding. These lesions are easily diagnosed by their appearance. However, some cancers develop slowly on the background of leukoplakia and present as superficially crusting, ulcerated lesions with little or no bulk and a history of repeated episodes of scab formation without complete healing. These lesions are not so easy to diagnose clinically, and only excisional biopsy provides the answer.

Erythema of the adjacent skin suggests dermal lymphatic invasion. Palpation of the lip reveals the extent of induration. Anesthesia or paresthesia of the skin of the lip indicates mental nerve invasion; however, nerve invasion may be encountered at operation or seen by the pathologist in the absence of symptoms.

Methods of Diagnosis and Staging

The differential diagnosis includes actinic cheilitis, leukoplakia, herpes simplex, keratoacanthoma, keratosis, syphilitic chancre, cysts, fibromas, myeloblastomas, benign mixed tumors, hemangiomas, pyogenic granulomas, and papillomas. The diagnosis is established by biopsy, or if the lesion is not discrete, a vermilionectomy (lip shave) may be done.

The AJCC staging for lip cancer includes only the lesions arising from those portions of the lips that oppose each other (ie, the dry vermilion).

Diagnostic Imaging

Few lip cancers require diagnostic imaging. It is usually a locally advanced, deeply infiltrating, or recurrent lesion that comes to imaging.

Computed tomography (CT) scanning in lip cancer patients is usually done to look for bone invasion. Axial CT scans with 2- to 3-mm slices, processed for bone detail, are useful for detecting subtle abnormalities along the buccal surface of the premaxilla and mandible. These may be augmented by multiplanar reformations designed for dental radiographic use (eg, DentaView; see section on cancers of the floor of the mouth in this chapter). Dental occlusal views, especially the submental vertex view, may also be valuable in evaluating the buccal and lingual surface of the maxilla and mandible. The alveolar ridge is best evaluated by use of Panorex and

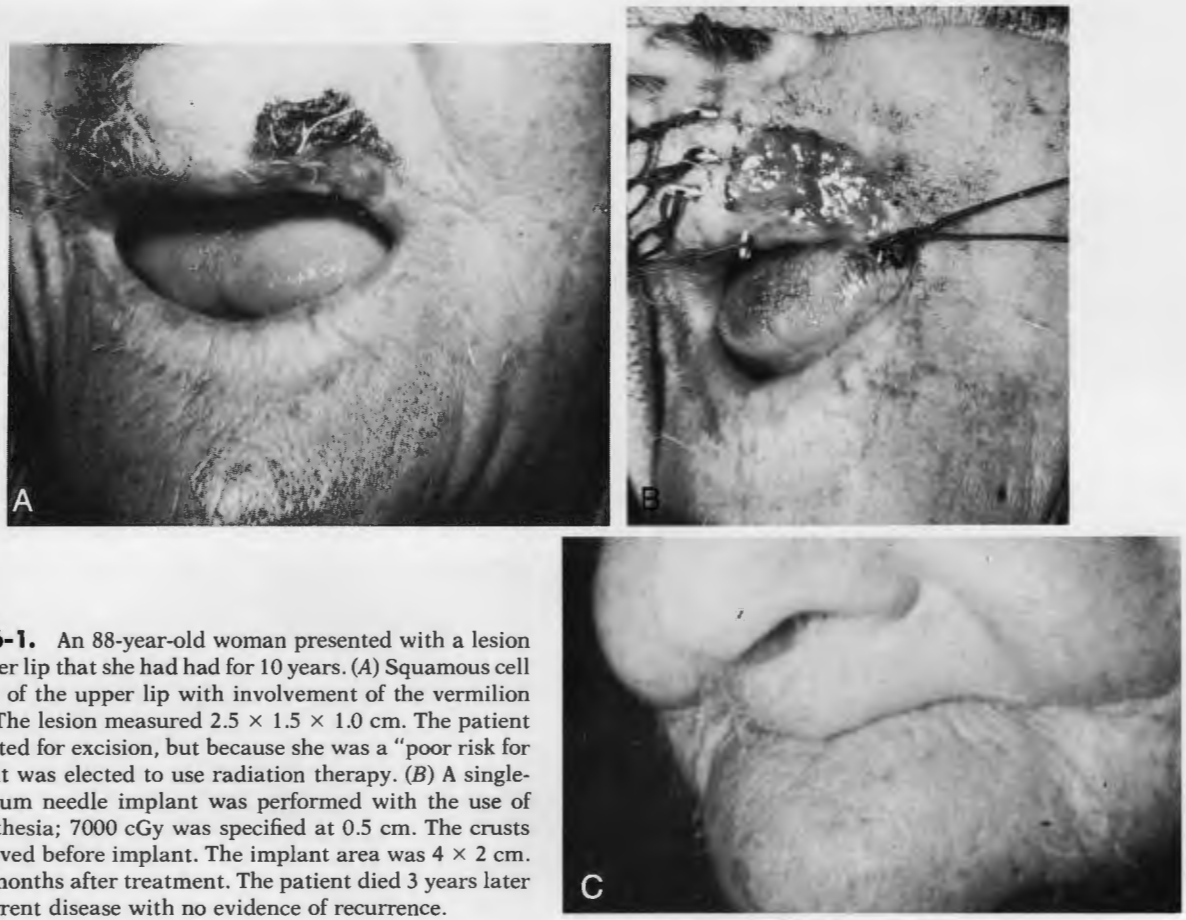


Figure 16-1. An 88-year-old woman presented with a lesion on the upper lip that she had had for 10 years. (*A*) Squamous cell carcinoma of the upper lip with involvement of the vermilion and skin. The lesion measured 2.5 × 1.5 × 1.0 cm. The patient was admitted for excision, but because she was a "poor risk for surgery," it was elected to use radiation therapy. (*B*) A single-plane radium needle implant was performed with the use of local anesthesia; 7000 cGy was specified at 0.5 cm. The crusts were removed before implant. The implant area was 4 × 2 cm. (*C*) Eight months after treatment. The patient died 3 years later of intercurrent disease with no evidence of recurrence.

other standard dental radiographic techniques. Magnetic resonance imaging (MRI) is of little or no use for detecting subtle bone erosion.

Patients who have deeply infiltrative recurrent tumor or signs or symptoms suggesting perineural invasion should have the entire course of the infraorbital and mandibular nerves studied. This evaluation should begin at the infraorbital and mental foramina, respectively, and follow the course of each nerve back to the cavernous sinus. This is probably best done with CT because these patients are often also at risk for bone erosion. If further evaluation is necessary, contrast-enhanced MRI might be necessary in highly selected cases to detect subtle perineural spread of tumor.

If lesions are sufficiently advanced to require imaging for possible bone erosion or perineural spread, it would be wise to include the regional nodes.

Treatment

Selection of Treatment Modality: Primary Site

LEUKOPLAKIA, HYPERKERATOSIS, CHEILITIS, CARCINOMA IN SITU. Superficial lesions are managed by vermilionectomy ("lip shave") with or without removal of a small cuff of muscle, depending on the thickness of the lesion. Vermilionectomy is used for diagnosis as well as treatment.

SQUAMOUS CELL CARCINOMA

Early Lesions (0.5 to 1.5 cm). The majority of small superficial lesions (2 to 3 mm thick and no longer than 2 cm) are surgically excised with primary closure as an outpatient procedure. Assuming a lower lip of 7 cm in length, excision of a 2-cm lesion with a 0.5-cm margin would result in a 4-cm lower lip, which could stretch with use. Surgery is satisfactory in these cases if it is not necessary to resect the lip commissure and if the resultant aperture of the oral cavity permits insertion of dentures. Excision provides an efficient outpatient treatment and is less expensive than either external-beam radiation therapy or an implant. Postoperative irradiation is recommended for positive margins or perineural invasion. Radiation therapy with either interstitial or external-beam techniques produces equal cure rates compared to surgery. Irradiation would be selected for lesions that would involve excision of the commissure and for all but the smallest lesions of the upper lip, because the cosmetic and functional result would be better (Figs. 16-1 and 16-2). The uncommon poorly differentiated lesion is preferably treated by radiation therapy in order to cover a more generous treatment volume and perhaps include the first-echelon lymph nodes (see also section on skin of the upper lip in Chap. 25).

Moderately Advanced Lesions (2 to 4 cm). The length of the lower lip is about 7 cm; it may be shorter in

(text continues on page 326)

Figure 16-2. A 72-year-old woman had a rapidly growing, moderately differentiated squamous cell carcinoma of the left upper lip. The globular lesion was 2.5 cm in diameter with induration in the lip extending to 3 cm maximum diameter. The maximum thickness was 1.5 cm. Radiation therapy was selected because of the large size and the extensive reconstruction that would be required after excision. (*A*) External-beam irradiation was used initially to flatten the lesion to facilitate the placement of an implant (3000 cGy over 3½ weeks, 170 cGy per day, 250 kV, Thoreus III). A lead shield (covered with a condom) was inserted under the upper lip (X). There was complete flattening of the very bulky lesion before radium implant with only residual induration and superficial ulceration remaining in the lip. The ink marks outline the external-beam portal, which included part of the columella and lateral ala nasi. (*B*) A single-plane implant was done using five, 2-cm active length needles held in a bar; two crossing needles were attached to the bar. A cylindrical pack was sutured behind the upper lip to displace the lip and radium from the upper gum; another pack was tied to the bar to space the lower lip away from the needles. (*C*) Moist desquamation 2 weeks after the implant. (*D*) Nearly complete healing at 5 weeks. (*E*) Two years after treatment, patient was free of disease.

Figure 16-3. A 46-year-old commercial fisherman first noted a lesion 14 months before treatment. Nine months before treatment, a biopsy showed no tumor, as did another biopsy 7 months before treatment. A third biopsy revealed well-differentiated epidermoid carcinoma of the lip. (*A*) The lesion was large and infected, involving the left commissure and three fourths of the lower lip. Induration extended from commissure to commissure and 2 cm beyond the gross lesion. There were small, mobile, firm submaxillary nodes that were considered positive. The lesion was staged T3N3B. Radiation therapy was elected because of the extent of disease. (*B*) The initial treatment consisted of 5000 cGy over 4½ weeks with orthovoltage (250 kV, Thoreus III). A lead shield was fashioned to outline the portal. An extension of the lead was fitted behind the lower lip to reduce transit irradiation. (*C*) The entire neck was irradiated with ^{60}Co, 5000 cGy over 5 weeks, using a single anterior field; the larynx was shielded. Treatment to the lip was completed with a single-plane radium implant using six vertical needles; 1500 cGy was added at 0.5 cm. The patient underwent bilateral supraomohyoid neck dissection because of the clinically positive nodes. Metastatic squamous cell carcinoma was found in one right neck node adjacent to the submandibular gland; there were no positive nodes in the left neck. A biopsy of the lip at the time of neck dissection showed no residual tumor. (*D*) Appearance 2½ years after treatment. Patient was free of disease at 6 years and was encouraged to wear a surgical mask while fishing.

edentulous patients. Removal of greater than half of the lower lip (ie, more than 3.5 to 4.0 cm) with simple closure often produces a relatively poor cosmetic and functional result and therefore requires a reconstructive procedure. If reconstruction is required, radiation therapy has the advantage of a better functional and cosmetic result with intact muscle and skin innervation. These larger lesions are managed by interstitial implantation, external-beam irradiation, or both (Fig. 16-3).

In summary, small lesions that do not involve the commissure or the upper lip can be simply managed with an outpatient surgical procedure and reconstruction either by primary closure or a simple flap from the upper lip. However, when the lesion reaches a size that requires the surgeon to use adjacent cheek tissue or distant or microsurgical flaps, radiotherapy is a better treatment. The reconstructed lip may look normal in a photograph, but the lip lacks sensory and motor innervation, and there is a loss of elasticity. Surgically treated patients more frequently have evidence of drooling, dribbling, difficulty in eating, and pain or altered lip sensation. Stranc and colleagues[76] studied lip function in 37 patients after surgery (19 cases) or radiotherapy (18 cases) and compared their findings to 29 normal controls. Their analysis showed that radiotherapy produces less loss of lower lip sensation, less loss of intercommissural distance while pursing the lips, and less loss of elasticity of the lip curtain than does an operation. Patients treated by radiotherapy showed values that were close to normal. Comparison of oral continence revealed that 2 of 18 patients who received radiotherapy complained of dribbling, whereas 8 of 19 treated surgically had difficulty in achieving a satisfactory lip seal. Difficulty with eating was noted in 3 of 19 surgical patients and none of the radiotherapy group. This difficulty was usually due to lack of sensation in the reconstructed lip, which made it difficult to monitor the presence or temperature of the food as it entered the mouth. The surgical patients compensated for this disability by using the tongue as a sensory organ.

Advanced Lesions. Advanced lesions may have extensive infiltration of neighboring skin and muscle, involvement of the labial commissure and buccal mucosa with extension to the upper lip, or invasion of the mandible and mental nerve. Large lesions without bone or nerve invasion are often managed initially with curative irradiation with operation reserved for persistence or recurrence. Lesions with invasion of bone or nerve are selectively managed by resection and postoperative radiation therapy. Erythema of the skin adjacent to the lesion usually indicates dermal lymphatic involvement (ie, "inflammatory carcinoma"), and wide-field irradiation is the initial treatment. Surgical resection may or may not be added, depending on the response to radiation therapy.

Management of the Neck

The regional lymphatics are not electively treated for early cases. Advanced lesions, poorly differentiated lesions, and recurrent lesions should have either elective neck irradiation or elective neck dissection, depending on the treatment selected for the primary lesion. Clinically positive nodes are usually managed by neck dissection with irradiation added according to policies outlined in Chapter 6.

Surgical Treatment

VERMILIONECTOMY. There are three basic types of vermilionectomy or lip shave. A simple excision of the vermilion to the orbicularis muscle is used for superficial lesions such as hyperkeratosis and leukoplakia, when there is no underlying induration (Fig. 16-4, *left*). A modified vermilionectomy includes a transverse wedge of the underlying orbicularis muscle and is usually used for carcinoma in situ, early superficial multicentric lesions, chronic cheilitis with some thickening of the vermilion, persistent noncancerous ulcers, and even a redundant lip (see Fig. 16-4, *center*). In many patients who have a squamous cell carcinoma of the lip, there are dysplastic changes on the remainder of the lower lip, and an excision of the lip lesion may be combined with a vermilionectomy. Vermilionectomy is done with the use of either a local infiltration anesthetic or a general anesthetic. The wet mucosa is advanced and sutured to the skin anteriorly. Initially, there is no sensation to the lip, and patients must be aware of the potential for burning the lip until sensation returns. In some cases, the procedure causes the skin edge to be everted toward the oral cavity, and the hair on the skin grows at such an angle that it causes an irritation of the upper lip or tongue

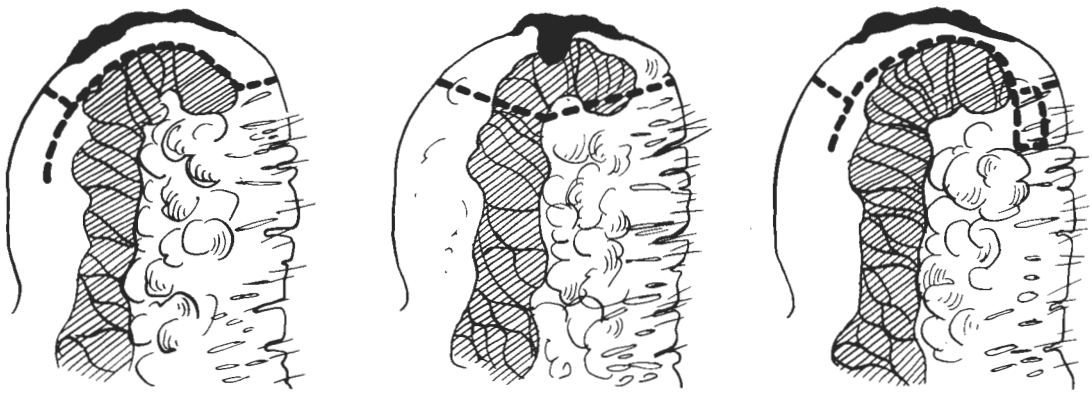


Figure 16-4. Vermilionectomy. (*Left*) Superficial lesion. Dry vermilion is excised down to muscle, and wet mucosa is advanced. Muscle is not removed. (*Center*) A small cuff of muscle is included if the lesion is suspicious for early invasion. (*Right*) The hair shafts are removed at the vermilion/skin junction to avoid annoying hair growth that accompanies the superior movement of skin.

when the lips are wetted. One or 2 mm of the deep layer of the dermis, which contains the hair follicles, can be excised at the time of lip shave to avoid this annoyance (see Fig. 16-4, *right*).

The complications of this procedure are usually minor and uncommon, and the cosmetic result is good. It would be rare to have a carcinoma develop on a resurfaced lip, unless carcinoma was present at the time of the resurfacing. One patient was seen who had developed a lip cancer 20 years after lip shave.

EXCISION. Surgical treatment for early lesions (0.5 to 1.5 cm) involves a W- or U-shaped excision (Fig. 16-5).[50] V-shaped excisions may be used for small lesions but do not give as good a margin for the larger tumors. Lesions larger than 1.5 cm may be closed with a full-thickness pedicle flap from the upper lip. If the vermilion is diffusely involved, with little or no involvement of the muscle, a vermilionectomy (lip shave) may be done at the time of excision. If the commissure must be sacrificed, it must be reconstructed to prevent microstomia and also to allow the edentulous patient enough opening to insert dentures.

RESECTION OF ADVANCED LESIONS OF THE LIP. Lip lesions that require 50% or greater removal of the lip require flap reconstruction. Various flaps are available for reconstruction of the lower lip, such as a rotational flap from the cheek or advancement flaps such as the Karapandzic flap (Fig. 16-6). Although the cosmetic results are generally good, all of these reconstructive procedures result in a smaller oral opening. Multiple reconstructive procedures are often necessary. If the lesion is tethered to the superior or anterior margin of the arch of the mandible without radiographic evidence of bone invasion, a rim resection may be performed in continuity with the lip lesion. Mandibulectomy is necessary when bone invasion occurs.

Irradiation Technique

Lip cancer is treated by external-beam irradiation, interstitial implants, or a combination of both (see Figs. 16-1 through 16-3 and 16-7 through 16-9).

Removable interstitial implants are done with sources such as radium, cesium, or iridium-192 (see Figs. 16-1 through 16-3 and 16-8).

External-beam techniques use orthovoltage (100 to 250 kV) or electrons; lead shields are placed behind the lip to limit oral cavity and mandible irradiation. The dose schemes are similar to those used for skin cancer (see Chap. 25). Fractionation schemes of 2 to 4 weeks are used for the smaller lesions; 4 to 6 weeks are preferred for the larger lesions to diminish the late effects of atrophy, telangiectasis, fibrosis, and ulceration. Large, infiltrative lesions may be first treated with external-beam irradiation, 3000 to 5000 cGy, and treatment is completed by interstitial therapy (see Figs. 16-2, 16-3, and 16-8). If the vermilion appears dysplastic, the entire lower lip may be treated with 80% of the dose required for the obvious lesion; the field size is reduced to cover the obvious lesion. A margin of 1.0 to 1.5 cm is sufficient for most early, discrete lesions.

Management of Recurrence

The patient with a recurrence is at significant risk to die of the disease. Small, localized recurrences occurring after initial surgery or radiation therapy are managed

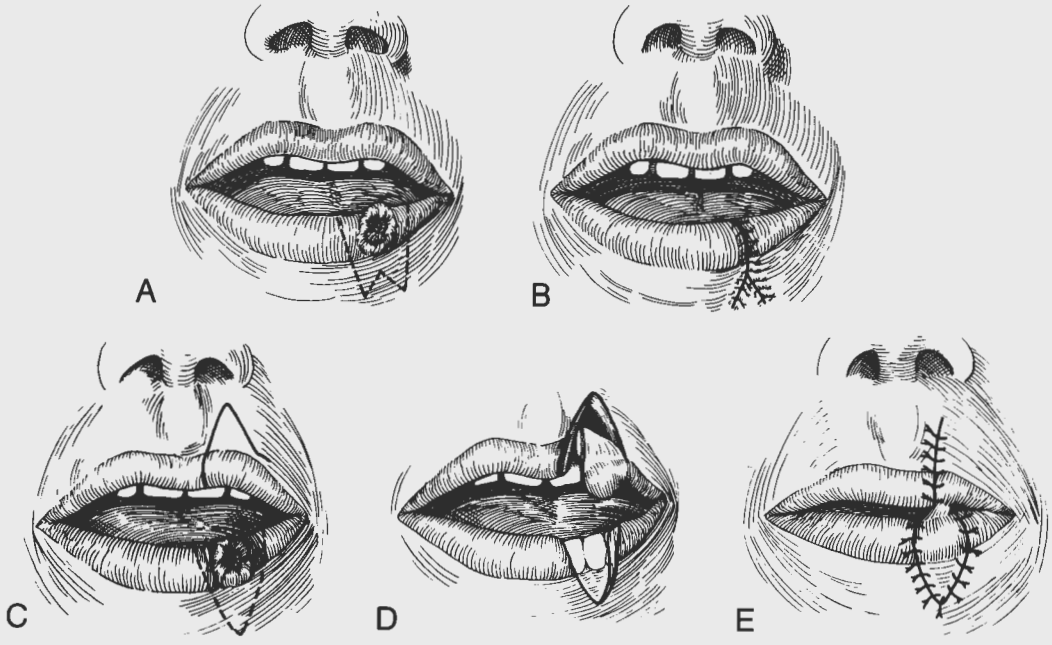


Figure 16-5. Small lip lesions not involving the oral commissure can be removed using a "W" excision (*A*) and closed primarily (*B*). Larger lesions of the lip may be removed in a "V" fashion (*C*) and the defect is closed using an Abbe flap from the upper lip (*D*), with a second procedure to release the flap 2 weeks later (*E*). (Million RR, Cassisi NJ, Clark JR. Cancer of the head and neck. In: DeVita VT Jr, Hellman S, Rosenberg SA, eds. Cancer: principles and practice of oncology, ed 3. Philadelphia, JB Lippincott, 1989:504)

Figure 16-6. (*A*) Discrete 2.5-cm squamous cell carcinoma of the lower lip. Ink marks indicate margins for "U" excision of lesion and extension of incision in preparation for advancement flaps. (*B*) Appearance after "U" excision of lesion. (*C*) Appearance after advancement of flaps from the left upper lip and remaining right lower lip. (*D*) Appearance 3 months after surgery. No revision was required, and function was essentially normal.

the same as previously untreated lesions. Most surgical failures are managed by radiation therapy because a large amount of lower lip would need to be resected (see Fig. 16-8). A combination of surgery and radiation therapy may be selected in certain situations (see Fig. 16-9). The regional lymph nodes, in particular, are more apt to be involved, and elective neck treatment is advised.

Results of Treatment

MacKay and Sellers[36] reviewed 2854 patients with all stages of lip cancer, of whom 92% were treated initially by radiation therapy. All patients had a minimum 5-year follow-up. The primary lesion was controlled by the initial treatment in 84% of cases, and an additional 8% were saved by later treatment, for an overall local control rate of 92%. Fifty-eight percent of those who presented with clinically involved nodes had control of disease, but the rate was only 35% when neck nodes appeared later. The cause-specific 5-year survival rate was 89%, and the absolute 5-year survival rate was 65%. Death due to intercurrent disease occurred in 17%. The M.D. Anderson Hospital local control rates for 444 previously untreated patients are shown in Table 16-2; 83% were managed initially by excision.[35] The 3- and 5-year cause-specific survival rate was 94%.

Teichgraeber and Larson[77] reviewed the M.D. Anderson Hospital experience for 46 patients with lip cancer that involved the commissure. Ten of 22 patients with T2

TABLE 16-2. Cancer of the Lip: Previously Untreated Patients (MD Anderson Hospital)

Size of Lesion	Treatment	Patients	Local Recurrence	Salvaged
0–1 cm	RT	30	0	—
	S	239	6	6
1–2 cm	RT	36	2	1
	S	116	3	1
>2 cm	RT	7	0	—
	S	7	3	0
Massive	RT	1	0	—
	S	8	1	0

RT = radiation therapy; S = surgery.
(Adapted from MacComb WS, Fletcher GH, Healey JE Jr: Intra-oral cavity. In MacComb WS, Fletcher FH, eds. Cancer of the head and neck, Baltimore, Williams & Wilkins, 1967:110)

TABLE 16-3. Squamous Cell Carcinoma of the Lip: 1953–1973 (University of Michigan)

Size of Lesion	Patients	Recurrence*	5-Year Survival	
			Cause-Specific	Absolute
<1 cm	85	10.6%	100%	76%
1–3 cm	154	9.1%	92%	71%
>3 cm	29	20.7%	71%	52%
Bone invasion	11	90.9%	50%	45%

* Treated by radiation therapy, 47%; treated by surgery, 53%.
(Modified from Baker SR, Krause CJ. Carcinoma of the lip. Laryngoscope 1980;90:22, 24)

lesions developed local recurrence, and 6 eventually died of disease. There are no data for commissure involvement treated by radiotherapy, but the relative ease of radiation treatment for commissure involvement and the resulting cosmetic and functional results that have been observed lead us to select radiotherapy for patients with this spread pattern.

Baker and Krause[6] reported treatment results from the University of Michigan; 47% of patients were treated by irradiation, and 53% were treated by operation. Excision with primary closure of the wound was the surgical management in 153 patients, whereas excision with a local flap was necessary in only 6 patients. Radiation therapy was used more commonly in the advanced lesions. The results of treatment are given in Table 16-3. The 5-year cause-specific and absolute survival rates for in situ, T1, and T2 tumors were essentially identical when comparing surgery and radiation therapy. Cervical metastasis occurred in approximately one third of the patients who developed local recurrence, emphasizing the need for elective neck treatment at the time of management of local recurrence.

Fitzpatrick[23] reported the results for 361 patients treated at the Princess Margaret Hospital in Toronto between 1971 and 1976. Table 16-4 shows local tumor control by therapy. Only 3% died of lip cancer. Mohs and Snow[53] reported the results for 1119 patients treated with microscopically controlled surgery between 1936 and 1976. Sixteen percent had been treated previously. The 5-year cause-specific cure rate was 94%. The cure rate declined from 97% for lesions less than 2 cm to 60% for 192 patients with lesions 2 cm or greater.

Petrovich and associates[61] reviewed 250 patients with carcinoma of the lip irradiated between 1966 and 1978.

TABLE 16-4. Carcinoma of the Lip–361 Patients (Princess Margaret Hospital, Toronto)

	Patients	Percent Local Control
Surgery	85	89%
Surgery plus radiotherapy	70	93%
Radiotherapy alone	206	94%
TOTAL	361	92%

(Modified from Fitzpatrick PJ. Cancer of the lip. J Otolaryngol 1984; 13:33)

The local control rate was 94% for 221 patients with stages I and II, 90% for stage III, and 47% for stage IV.

Thirty-one patients were treated by radiation therapy for recurrent lip cancer after one or more operations. The results according to site of recurrence are shown in Table 16-5. Eight patients had perineural invasion, and only one is alive with no evidence of disease at 41 months. Six patients had bone invasion, and all were dead within 2 years. The 5-year absolute and cause-specific survival rate was 38% (Nichols RC, unpublished data, October 1989).

Follow-Up Policy

About 20% of local and regional recurrences appear after 5 years, and approximately 5% of the patients develop completely new lip cancers.

Patients are seen for examination every 1 to 2 months for 2 years, every 3 to 4 months for the third year, and every 6 months thereafter.

Complications of Treatment

Surgical Treatment

Microstomia and drooling secondary to oral incompetence may occur when a large flap reconstruction is necessary, especially if the commissure is resected. If the oral opening is reduced in size, dental care, denture fabrication, and peroral intubation may be compromised. Speech may be affected because of loss of motor function of the reconstructed lip. The cosmetic result is usually good after excision of small lesions or after small flap reconstruction of lesions not involving the commissure, but the appearance is impaired with reconstruction of larger lesions, particularly those previously irradiated. Difficulty in eating may occur as a result of loss of sensation.

Radiation Therapy

There will be some atrophy of the irradiated tissues. Continued exposure to the elements may result in a soft tissue necrosis; this problem is reduced by treatment schemes that prolong the treatment. The irradiated lip must be protected from sun exposure by use of hats and ultraviolet protectants. Fishermen and boaters should consider wearing a surgical face mask while on the wa-

(*text continues on page 333*)

TABLE 16-5. Recurrent Lip Cancer Treated by Irradiation: Results According to Site of Recurrence (31 Patients)

Sites Involved	Continuous Control Above the Clavicles*	5-Year Cause-Specific Survival
Primary alone	5/10	5/11
Primary and neck	6/15	5/15
Neck alone	1/3	1/3

* Two-year minimum follow-up.
Note: University of Florida data; patients treated October 1964 to October 1987; analysis October 1989 by R Charles Nichols, MD.

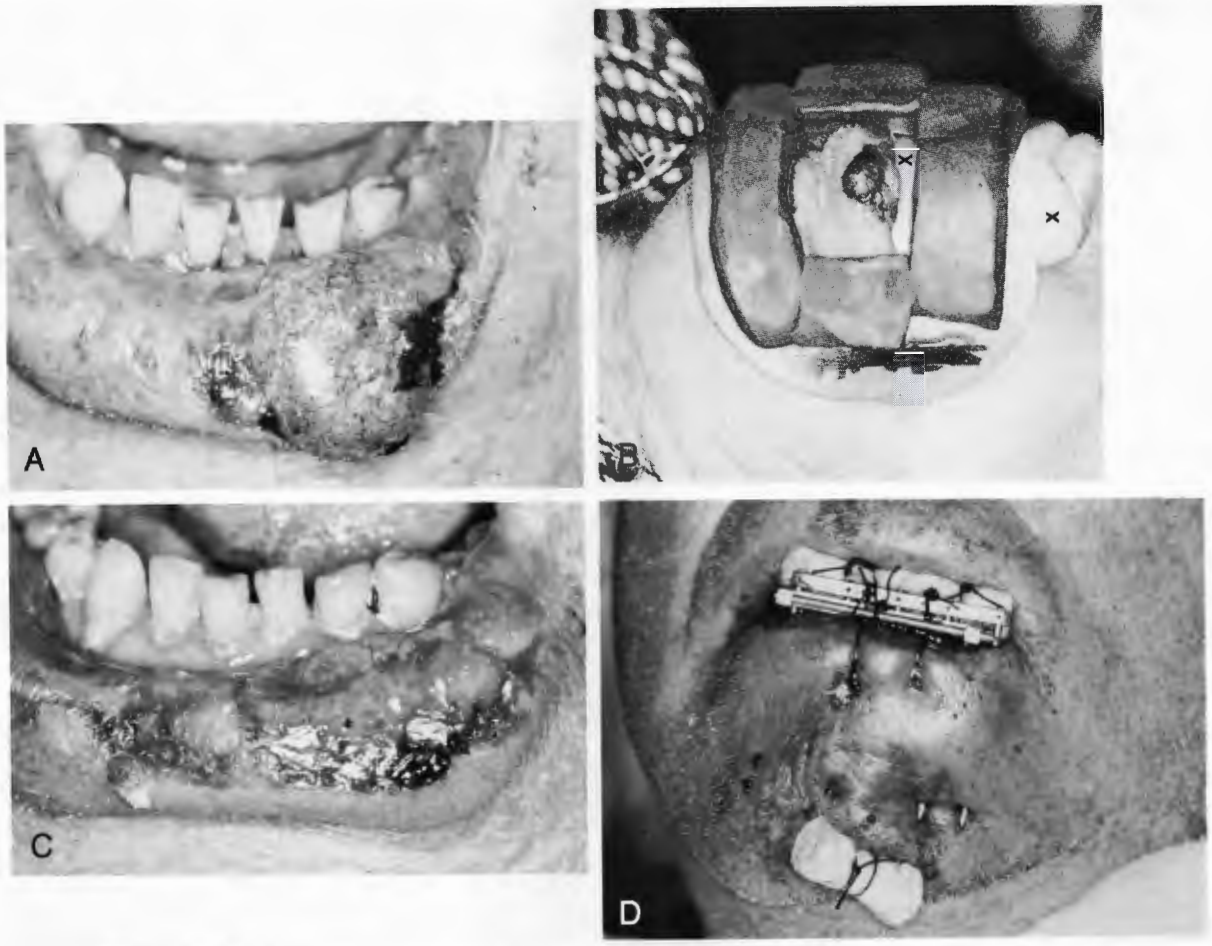
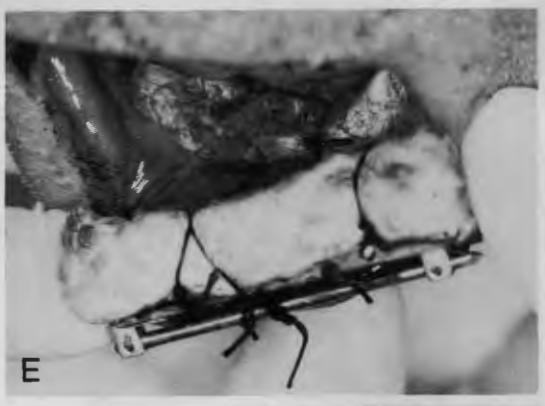
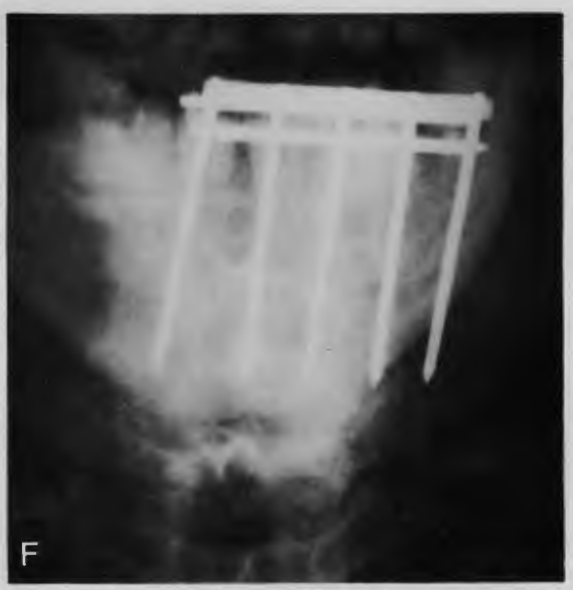


Figure 16-7. A 67-year-old man had a T2N0 squamous cell carcinoma of the lower lip. (*A*) The lesion measured 3.0 × 2.0 × 1.5 cm. Radiation therapy was elected because of the functional deficit likely to result from excision of the large lesion. (*B*) A 2-mm thick, lead mask was designed to outline the portal. A separate lead shield covered with beeswax was inserted behind the lower lip (*X*). He received 3000 cGy over 2 weeks, 300 cGy per fraction, 250 kV (0.5 mm Cu). Lead putty was added to the shield to reduce transit irradiation to less than 1%. (*C*) By the completion of 3000 cGy, he had a brisk mucositis of the lip and 60% to 70% regression of the obvious tumor. (*D*) A single-plane radium needle implant with double crossing. A gingivolabial pack was tied to the top of the bar to displace the upper lip. A chin pack was used to anchor the gingivolabial pack in place (see *E*). (*E*) A gauze pack was sewn into the gingivolabial gutter to displace the radium from the mandible and upper lip. (*F* and *G*) Roentgenograms of implant. The implant added 3500 cGy at 0.5 cm. (*H*) At 2½ weeks after implantation, there was superficial ulceration. (*I*) At 3 years, 8 months, there was no evidence of disease and the lip was completely healed.





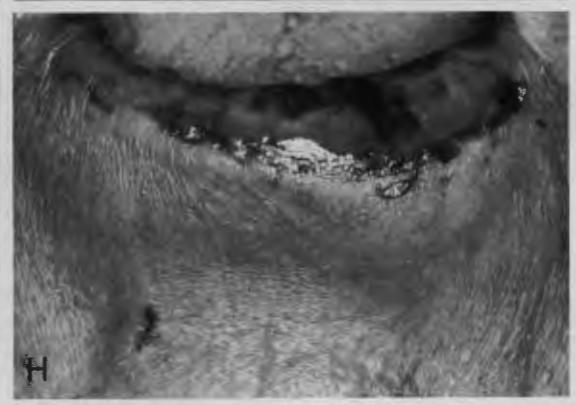


Figure 16-7. (*Continued*)

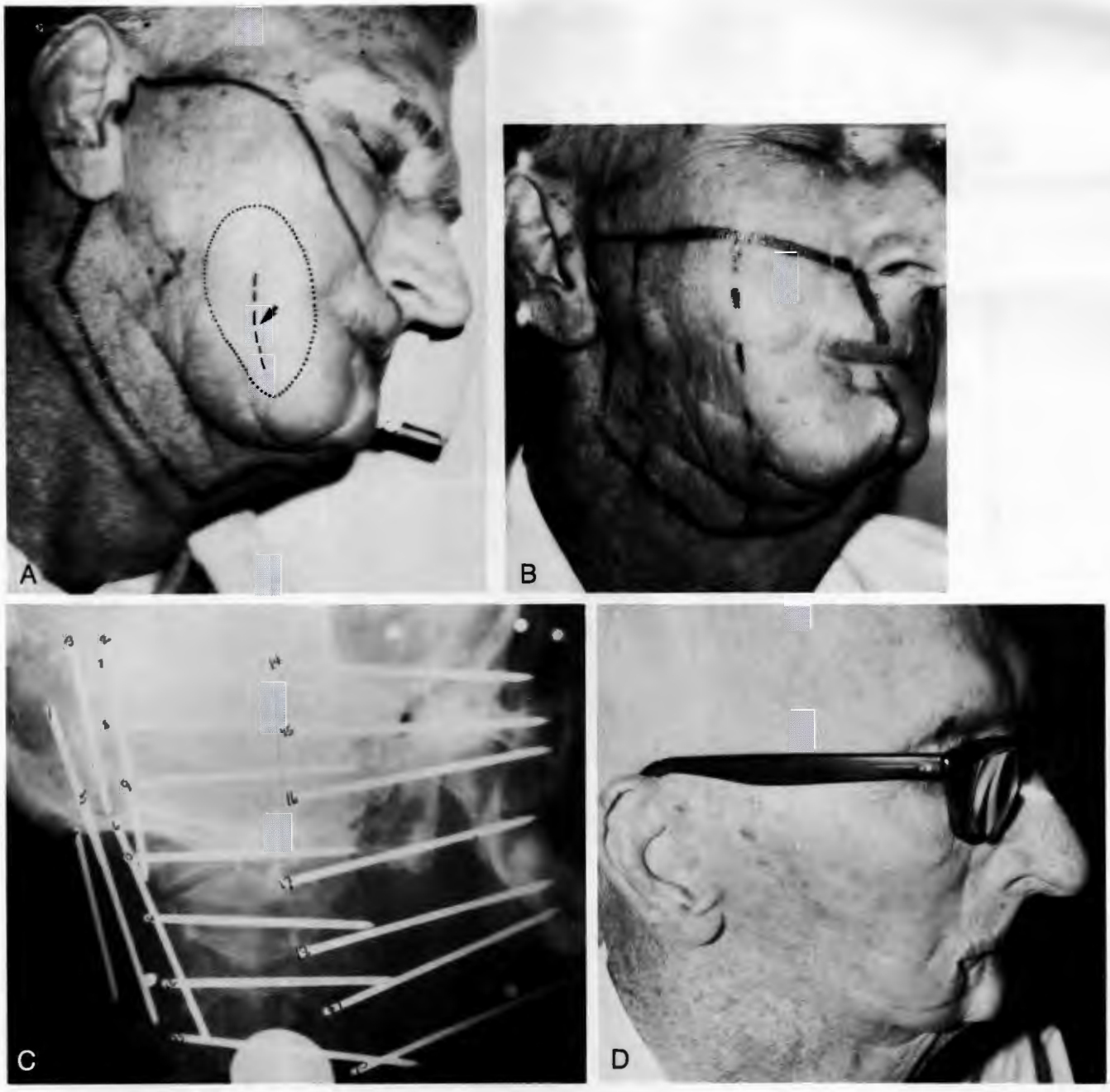


Figure 16-8. A 64-year-old man was first treated in 1969 by electrocautery and wedge resection for squamous cell carcinoma of the right lower lip. Four years later, he had a recurrence that required a right hemimandibulectomy with flap reconstruction. He had two more reconstructive procedures the same year. In 1974, he was admitted for a bone graft to bridge the right mandibular defect. At the time of surgery, recurrent epidermoid carcinoma was noted. (*A*) The arrow indicates the site of positive biopsy. The dotted line indicates the area of palpable recurrent disease. The solid line is the outline of the radiation therapy portal. The entire neck was electively irradiated. The patient received 5000 cGy tumor dose over 8½ weeks, split course, ^{60}Co. (*B*) A large single-plane implant was planned to deliver 1500 cGy at 0.5 cm. The solid lines outline the borders for the radium needle implant. (*C*) Roentgenogram of implant. (*D*) Patient was free of disease 8 years after treatment (appearance at 7 years). Long-term salvage in this type of recurrence is unusual.

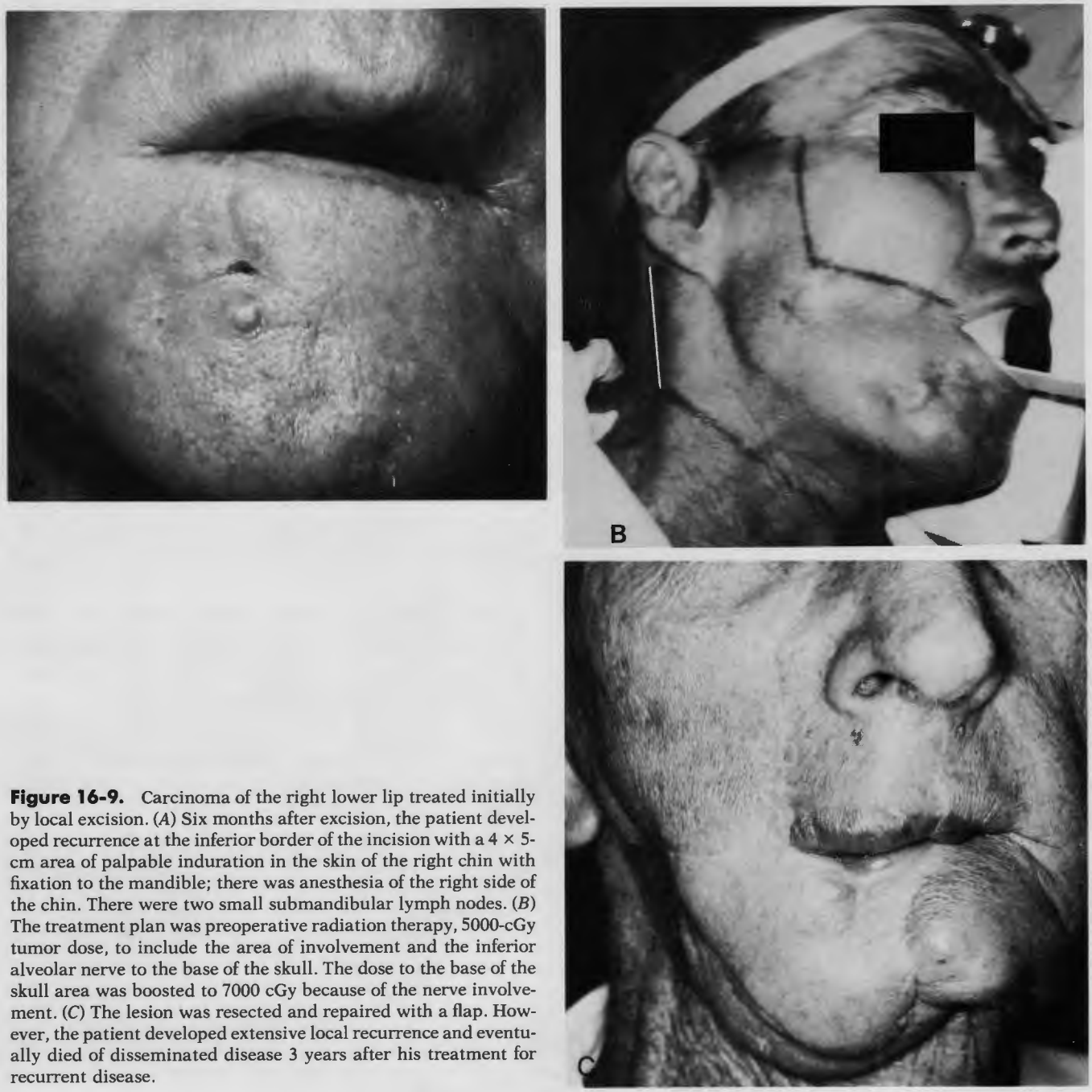


Figure 16-9. Carcinoma of the right lower lip treated initially by local excision. (*A*) Six months after excision, the patient developed recurrence at the inferior border of the incision with a 4 × 5-cm area of palpable induration in the skin of the right chin with fixation to the mandible; there was anesthesia of the right side of the chin. There were two small submandibular lymph nodes. (*B*) The treatment plan was preoperative radiation therapy, 5000-cGy tumor dose, to include the area of involvement and the inferior alveolar nerve to the base of the skull. The dose to the base of the skull area was boosted to 7000 cGy because of the nerve involvement. (*C*) The lesion was resected and repaired with a flap. However, the patient developed extensive local recurrence and eventually died of disseminated disease 3 years after his treatment for recurrent disease.

ter, because the various ultraviolet protectants do not adhere well to the lip (see Chap. 25).

The anterior teeth and gingiva are protected by lead shields when treatment is given by external-beam irradiation. Radiation caries, bone exposure, and rarely osteoradionecrosis are uncommon late sequelae of interstitial therapy. Fitzpatrick[23] reported a 3.3% incidence of late effects that required surgical intervention.

FLOOR OF THE MOUTH

Anatomy

The floor of the mouth is a U-shaped area bounded by the lower gum and the oral tongue; it terminates posteriorly at the insertion of the anterior tonsillar pillar into the tongue. The paired sublingual glands lie immediately

below the mucous membrane. The glands are separated by the paired midline genioglossus and geniohyoid muscles. Bony protuberances, the genial tubercles, occur at the point of insertion of these two muscle groups on the symphysis (Fig. 16-10). They may be prominent and easily palpable in some patients and interfere with the placement of interstitial sources. The mylohyoid muscle arises from the mylohyoid ridge of the mandible and is the muscular floor for the oral cavity. The mylohyoid muscle ends posteriorly at about the level of the third molars. The normal submandibular gland is about the size of a walnut. Most of the gland rests on the external surface of the mylohyoid muscle in the niche between the mandible and the insertion of the mylohyoid. A tongue-like process wraps around the posterior border of the mylohyoid muscle and extends forward on the internal surface of the mylohyoid. This process is absent in 10% to 20% of cases. In older patients, the submandibular gland is more prominent, is palpated slightly lower in the neck, and is more easily palpated. The glandular tissue atrophies with age and is largely replaced by fat, similar to the parotid gland. The submandibular duct (Wharton's duct) is about 5 cm long. It courses between the sublingual gland and the genioglossus muscle and exits in the anterior floor of mouth near the midline. The relationships of the lingual nerve, hypoglossal nerve, and submandibular duct are shown in Figure 16-10. The lingual nerve provides the sensory pathway to the floor of the mouth. The arterial supply is through the lingual artery, the second branch of the external carotid.

Imaging of the Normal Anatomy

Normal axial MRI anatomy of the oral cavity and oropharynx is shown in Figures 16-11 and 16-12.[39] On CT and MRI axial images through the floor of the mouth and oral tongue, the lingual septum is seen as a fat-containing space lying between the paired bellies of the genioglossus and geniohyoid muscles. This represents no significant boundary to tumor spread. Likewise, there is potential for communication across the midline in the potential space between the inferior margin of the genioglossus and geniohyoid muscles and the space below the geniohyoid muscle. The genioglossus and geniohyoid muscles form the medial boundary of the sublingual space; the mylohyoid muscle forms the lateral boundary. The mylohyoid muscle is best seen on coronal sections as it extends from the mylohyoid line of the mandible to the hyoid bone. On axial sections, the mylohyoid is seen as a thin band of muscle tissue along the lateral aspect of the sublingual space separating it from the submandibular space; the sublingual spaces usually appear symmetric. The submandibular space is in the suprahyoid portion of the neck and is separated from the floor of the mouth by the mylohyoid muscle. The mylohyoid muscle, therefore, separates the neck and the floor of the mouth (Fig. 16-13).[38] Because these spaces contain glandular and fatty tissue, they are easily distinguished from adjacent muscles both on CT and MRI. The lingual vessels are seen coursing within these spaces. The hypoglossal nerve and lingual nerve are not normally visible. The expected positions of the lingual and hypoglossal nerves are predictable based on their relationship to the hyoglossus muscle. The hyoglossus muscle is routinely seen on axial and coronal images as a thin band of muscle tissue coursing within the glandular and fatty tissue of the sublingual space. The lingual nerve and submandibular duct lie lateral to the hyoglossus muscle along with the sublingual gland. The lingual artery and vein course medial to the hyoglossus muscle, and the hypoglossal nerve lies in close proximity, forming the main neurovascular bundle of the tongue.

The anterior belly of each digastric muscle lies below the mylohyoid muscle, and, anteriorly, the small space lying between the digastric muscles near their insertion on the mandible is the submental space. The submandibular space contains the submandibular gland, facial vessels, and lymph nodes. Lymph nodes lie in the fat anterior and posterior to the gland as well as along the course of the facial vessels as they cross over the midportion of the submandibular gland. There are normally small (less than 5 mm) lymph nodes in the submental space as well.

The mylohyoid muscle ends at its posterior attachment to the mylohyoid line of the mandible at approximately the level of the posterior extent of the floor of mouth and the retromolar trigone. Here, the deep process of the submandibular gland usually juts over the

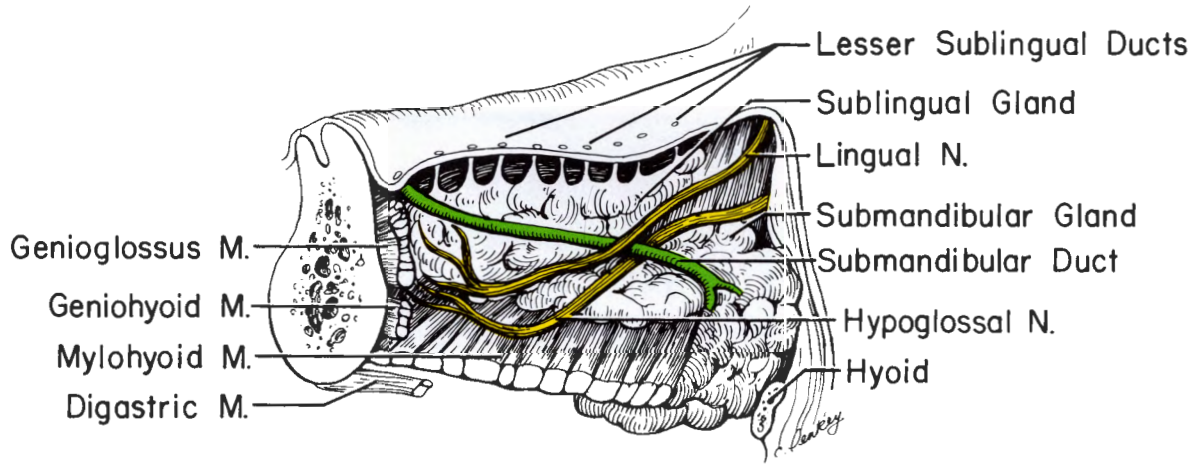


Figure 16-10. Anatomic relationships of the floor of the oral cavity. (Million RR, Cassisi NJ, Clark JR. Cancer of the head and neck. In: DeVita VT Jr, Hellman S, Rosenberg SA, eds. Cancer: principles and practice of oncology, ed 3. Philadelphia, JB Lippincott, 1989:506)

posterior free edge of the mylohyoid muscle to come in contact with the posterior aspect of the sublingual gland.

The lingual and buccal surfaces of the mandible are well seen on axial and coronal images. Bony landmarks include the mandibular foramen, the mental foramen, and the genial tubercles for the insertion of the genioglossus and geniohyoid muscles. The muscles of mastication, attached both medially and laterally with their encompassing fascia, form the masticator space.

Pathology

The majority of neoplasms are squamous cell carcinoma, usually of moderate grade. Adenoid cystic and mucoepidermoid carcinomas account for 2% to 3% of malignant tumors in this area.

Patterns of Spread

Primary

Approximately 90% of neoplasms originate within 2 cm of the anterior midline floor of the mouth. They penetrate early beneath the mucosa into the sublingual gland and the midline genioglossus and geniohyoid muscles. The mylohyoid muscle acts as an effective barrier until the lesion becomes advanced. Extension toward the gingiva and periosteum of the mandible occurs early and frequently. Even small lesions become attached to the periosteum. The periosteum is an effective barrier to mandibular invasion; when tumor reaches the periosteum, the tumor first spreads along the periosteum rather than through it. Mandible invasion is usually a late manifestation. The tumor often grows along or over the alveolar ridge before it grossly invades bone. The lower lip may be involved in advanced cases. Posterior extension occurs into the muscles of the root of the tongue; this pattern of extension is usually associated with ulceration of the floor of the mouth and undersurface of the tongue.

One or both submandibular ducts are frequently obstructed by a tumor, and the enlarged duct may be palpated through the floor of the mouth. It is difficult to distinguish between tumor extension and low-grade infection in an obstructed duct. Tumor rarely grows inside the duct but may grow along the path of the duct and may grow around the neurovascular bundle of the tongue. The submandibular gland frequently enlarges when the duct is obstructed and becomes firm and occasionally painful. It is impossible to distinguish by palpation between tumor involving the gland and chronic infection related to obstruction.

Tumors arising in the lateral floor of mouth are less common but have the same general spread patterns. Extensive lesions may escape the oral cavity by following the anatomic plane of the mylohyoid muscle to its posterior extremity, emerging in the neck near the angle of the mandible.

Lymphatics

Approximately 30% of patients have clinically positive nodes on admission; 4% have bilateral nodes. Nodal and submandibular gland enlargement secondary to low-grade inflammation is common and complicates physical diagnosis. CT examination helps in the diagnosis, particularly with the submandibular gland. The distribution of nodal metastases on admission is shown in Figure 16-14.[34] The reported incidence of conversion of the neck nodes from clinically negative to clinically positive with no neck treatment varies from 20% to 35%.[5,15,18,48]

For 62 patients with carcinoma of the floor of the mouth, the distribution of involved lymph nodes after elective neck dissection is shown in Figure 16-15.[13] The incidence of involved lymph nodes was 19% for patients with T1 or T2 lesions and 26% for patients with T3 and T4 lesions.

Several authors have correlated histologic features with the risk of metastatic disease in lymph nodes.[52,54,70,75] The depth of invasion, the character of the tumor–normal tissue boundary (ie, well-demarcated versus diffuse invasion at the boundary), lymphatic or vascular space invasion, and the degree of inflammatory (lymphoplasmocytic) response are just as predictive of lymph node metastasis as tumor diameter and grade. Table 16-6 correlates the risk of lymph node metastasis with the thickness of the lesion for 84 patients with stage I and II carcinoma of the floor of the mouth. There are slight differences between the various reports, but a tumor thickness in the range of 2 to 4 mm correlates with a rapid increase in the risk of lymph node metastasis.

The first nodes involved are the submandibular and the subdigastric nodes. The submental nodes are bypassed in most cases; Lindberg[34] reported 2% clinically positive submental nodes in 258 cases, and Byers and coworkers[13] reported a similar low rate for elective neck dissection (see Fig. 16-15). The risk of bilateral clinically positive lymph nodes was only 6% on admission. However, because most lesions either approach or cross the midline, the risk for bilateral spread is high. Fletcher[24] reported that 47% of patients (9 of 19) with ipsilateral positive lymph nodes (N1 or N2) developed contralateral neck disease if no elective neck treatment was given. This rate was reduced to 10% (3 of 28) after 3000 to 4000 cGy was given to the upper neck.

Clinical Picture

Presenting Symptoms

Early carcinomas are asymptomatic, red, slightly elevated mucosal lesions with ill-defined borders. Red lesions 1 to 5 mm in diameter have an equal chance of being carcinoma in situ or invasive carcinoma; lesions measuring 6 mm to 2 cm are more likely (3 : 1) to be

(*text continues on page 341*)

TABLE 16-6. Floor of Mouth Carcinoma, Stage I and II: Risk of Neck Disease (East Orange VA Medical Center)—84 Patients

Thickness (mm)	Stage I	Stage II	Total
0.1–1.5	1/38	0/19	1/57
1.6–3.5	1/5	3/7	4/12
3.6 or more	7/11	2/4	9/15

(Adapted from Mohit-Tabatabai MA, Sobel HJ, Rush BF, Mashberg A. Relation of thickness of floor of mouth stage I and II cancers to regional metastasis. Am J Surg 1986;152:352)

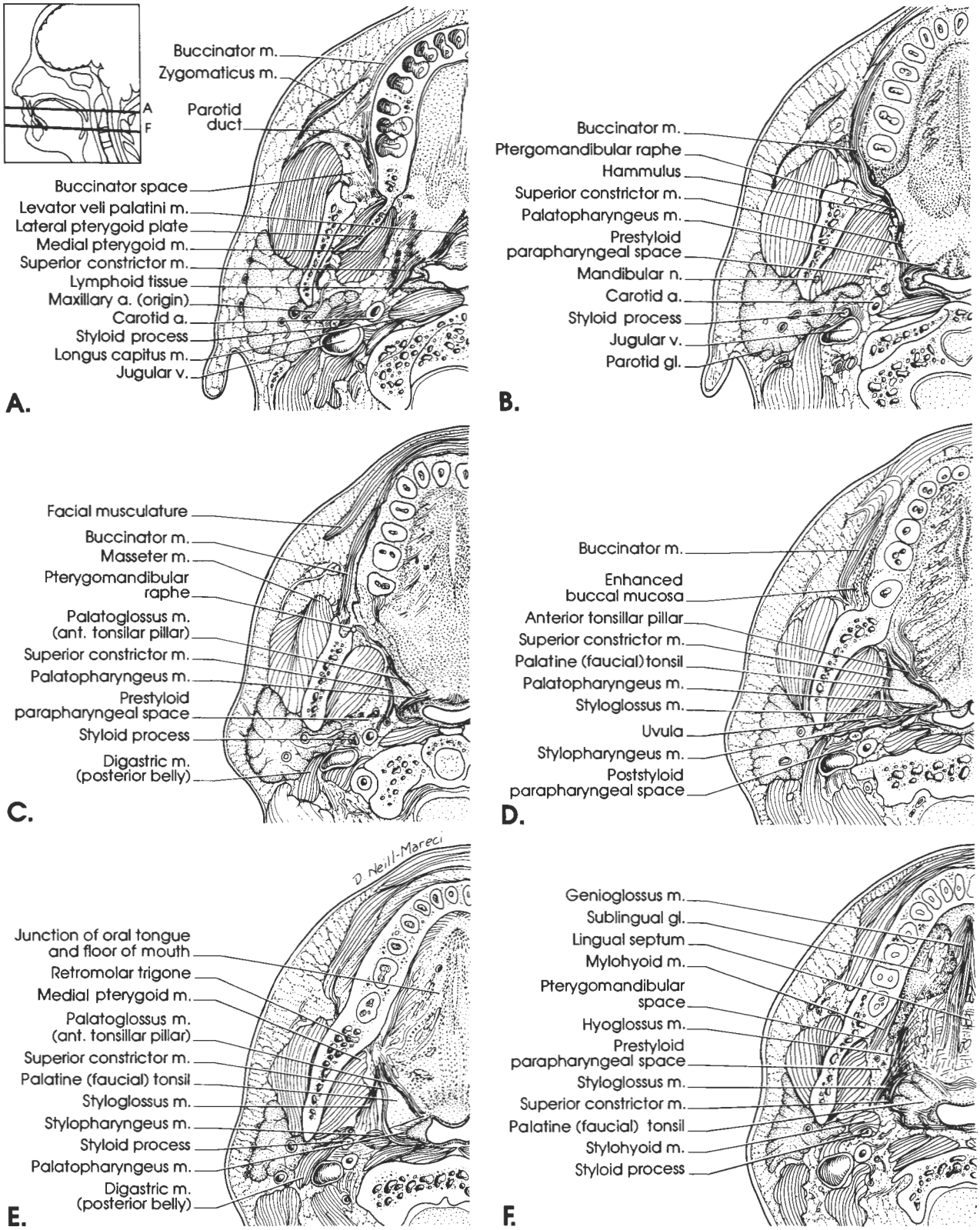


Figure 16-11. (*A* through *F*) Anatomic line diagrams from the upper to mid oropharynx, including the oral cavity, to correlate with the accompanying MR images at the same levels. (Mancuso AA, Harnsberger HR, Dillon WP. Workbook for MRI and CT of the head and neck, ed 2. Baltimore, Williams & Wilkins, 1989:156–157)

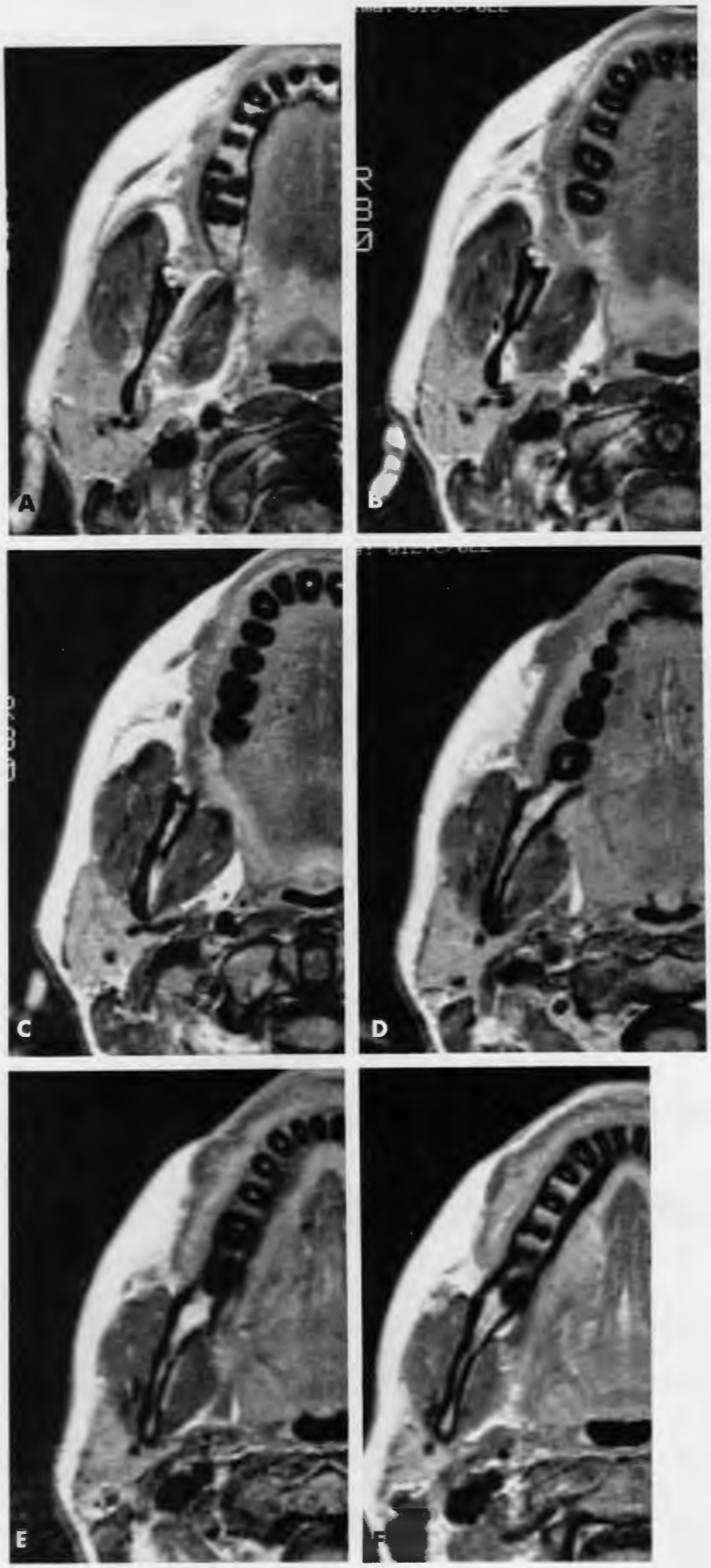


Figure 16-11. (*Continued*)

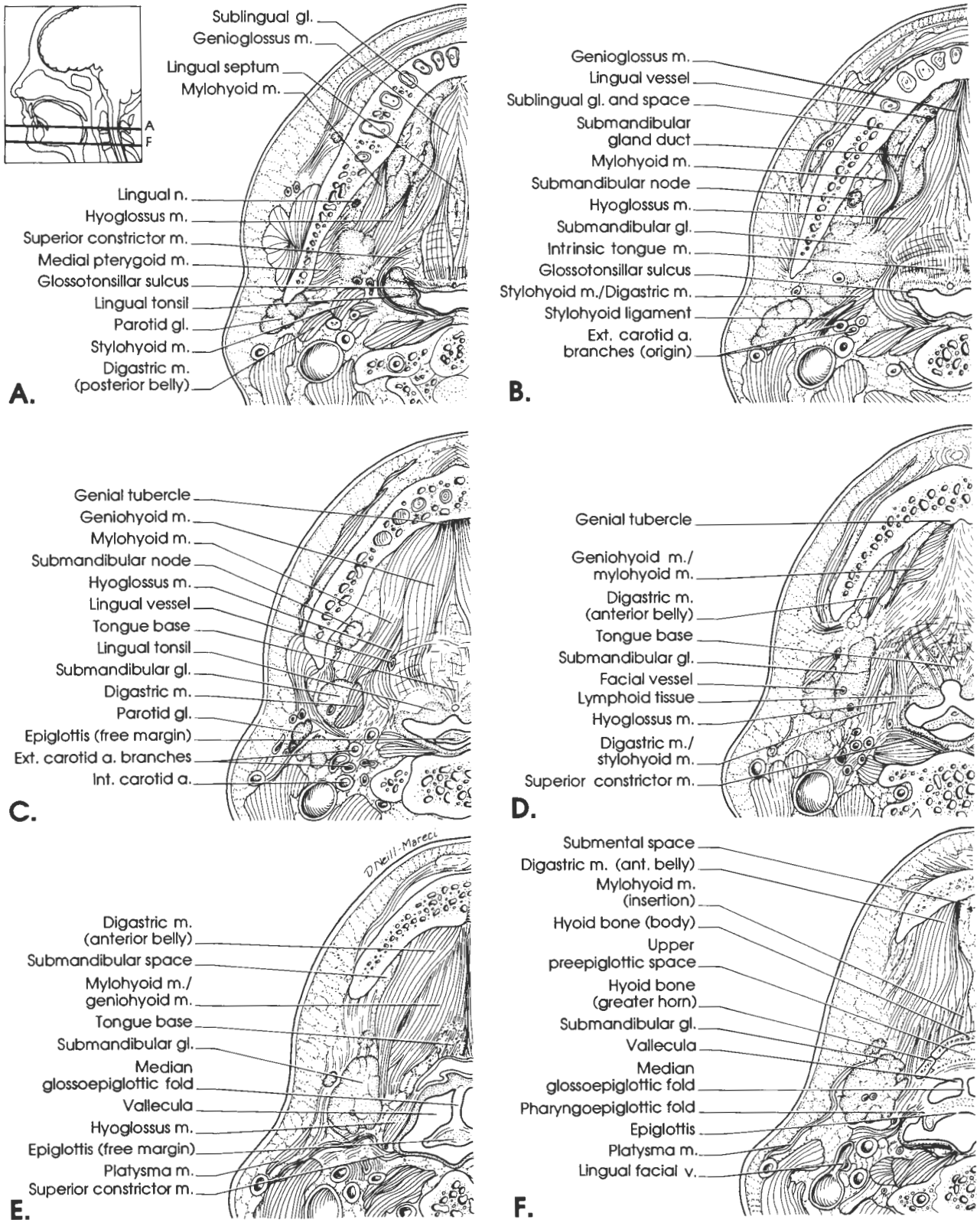


Figure 16-12. (*A* through *F*) Anatomic line diagrams from the mid oropharynx to the level of the valleculae, including the floor of the mouth, to correlate with the accompanying MR imaging at the same levels. (Mancuso AA, Harnsberger HR, Dillon WP. Workbook for MRI and CT of the head and neck, ed 2. Baltimore, Williams & Wilkins, 1989:156–157)

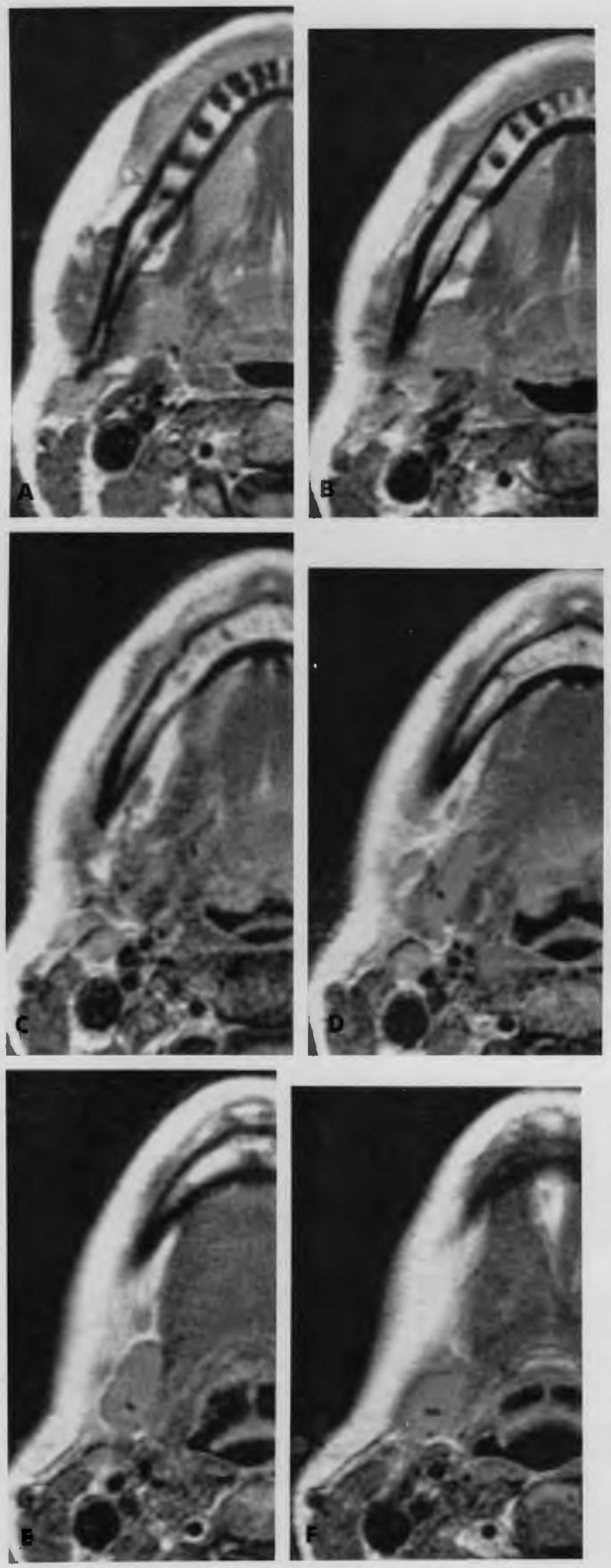
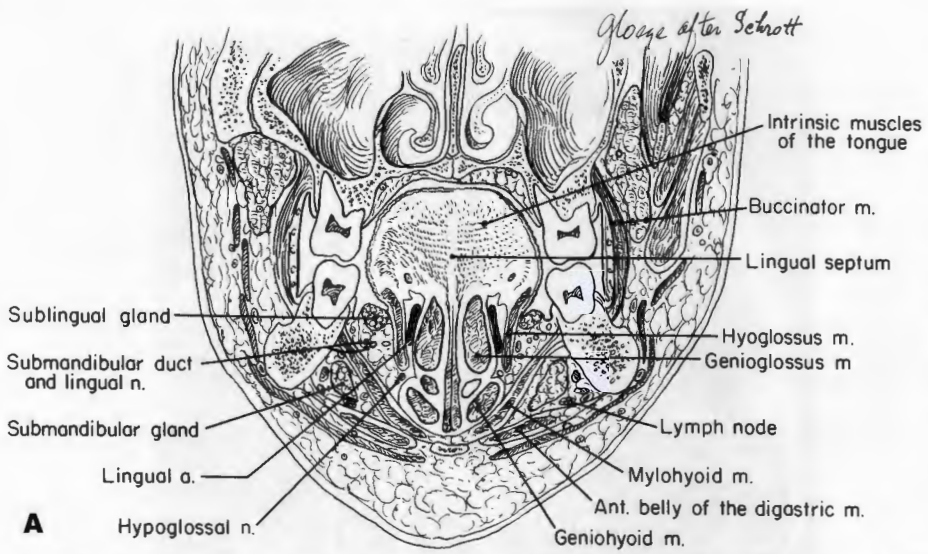


Figure 16-12. (*Continued*)



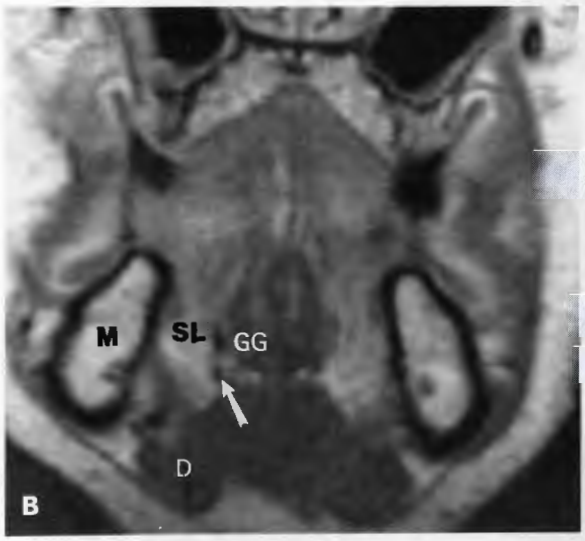
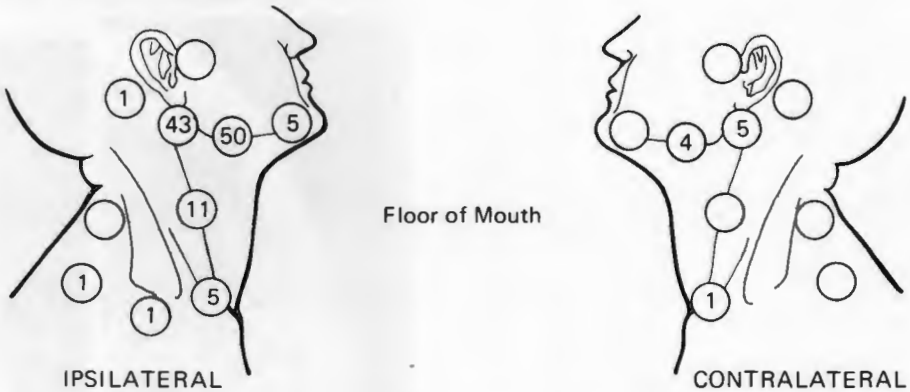


Figure 16-13. (*A*) Coronal line diagram showing the major anatomic relationships of the oral cavity, floor of the mouth, and suprahyoid neck. (*B*, *C*) Coronal MRI sections through the anterior and mid oral cavity and floor of the mouth showing the major spaces, muscles, and salivary glands as well as the positions of neurovascular bundles shown in *A*. M, mandible; SL, sublingual space; GG, genioglossus muscle; D, digastric muscle; arrow, lingual vessels; SM, submandibular space; MH, mylohyoid muscle; arrowhead, hyoglossus muscle. (Mancuso AA, Hanafee WN. Computed tomography and magnetic resonance imaging of the head and neck, ed 2. Baltimore, Williams & Wilkins, 1985;359)



N_0	N_1	N_{2A}	N_{2B}	N_{3A}	N_{3B}	N_1–N_3 / Total
179	38	4	17	9	11	79 / 258=30.5%

Figure 16-14. Carcinoma of the floor of the mouth: nodal distribution on admission, MD Anderson Hospital, 1948 to 1965. (Lindberg RD. Distribution of cervical lymph node metastases from squamous cell carcinoma of the upper respiratory and digestive tracts. Cancer 1972;29:1448)

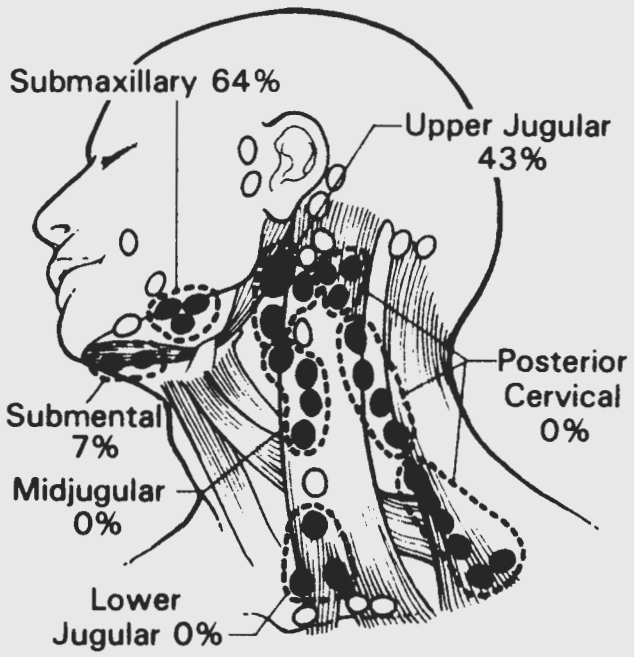


Figure 16-15. The distribution of involved neck nodes in the N0 neck when electively dissected for 62 patients with carcinoma of the floor of the mouth. (Byers RM, Wolf PF, Ballantyne AJ. Rationale for elective modified neck dissection. Head Neck Surg 1988;10:162)

invasive, and nearly all red lesions over 2 cm in diameter are invasive.[41] A background of leukoplakia may be present. White lesions (leukoplakia) are less likely to be malignant, but 17.5% are said to become cancer with long follow-up.[71] These lesions are usually diagnosed by the dentist or physician on routine oral examination.

T1 and T2 tumors are first noticed when the patient feels a lump in the floor of mouth with the tip of the tongue. There is mild soreness when eating or drinking that is usually thought by the patient (and sometimes the physician) to be due to a canker or denture sore. Advanced lesions produce pain, bleeding, foul breath, loose teeth, change in speech due to fixation of the root of the tongue, and a submandibular mass, which is often painful. Pain may be referred to the ear (Fig. 16-16).[51]

Physical Examination

The earliest lesions appear as a red area, slightly elevated, with ill-defined borders and little induration. As the lesion enlarges, the edges of the tumor become distinct, elevated, and "rolled" with a central ulceration and induration.

Some lesions start with a background of leukoplakia. If the leukoplakia is extensive, it is difficult to know where or when to perform biopsy.

Bimanual palpation determines the extent of the induration and the degree of fixation to the periosteum. Large lesions bulge into the submental space and rarely grow through the mylohyoid muscle into the soft tissues of the neck and even the skin. The submandibular duct and gland are evaluated by bimanual palpation.

Methods of Diagnosis and Staging

Biopsy Technique

Small (5 mm) discrete lesions should be completely excised for diagnosis and cure; the margins of the resected lesion must be tagged by sutures and carefully examined by frozen section for adequate margins. If frozen section is not done and the permanent sections show close or positive margins, the opportunity for precise reexcision has been lost. The deep margin is the one most often positive. For larger lesions, an incisional or punch forceps biopsy is used.

Diagnostic Imaging

The radiologist helps with three basic categories of information in patients with floor of the mouth cancer, including (1) the status of the mandible and related teeth, (2) the deep extent of the primary tumor, and (3) the status of the regional lymph nodes. Superficial, low-volume lesions do not need to be studied. A good rule of thumb is that lesions with any clinical evidence of deep infiltration or possible tethering to the mandible should be imaged. CT is the first choice because the mandible and regional nodes are of prime interest. In selected cases, a supplemental focused MRI study might be useful to define clearly the deep extent of the primary tumor when it is uncertain on CT. Ultrasound and radionuclide studies are rarely used because they do not produce important incremental information.

Questions concerning the status of the patient's dentition are best handled by a combination of orthopantography and standard dental views. Oblique views of the mandible may be included to help the surgeon decide whether there is enough mandibular bone stock present to allow for a rim resection; such evaluation is usually most critical in edentulous patients. These radiographic studies are also valuable to assess possible bone erosion involving the mandibular alveolar ridge. CT is the best study for evaluating the lingual and buccal surfaces of the mandible. The study should be done with 2- to 3-mm thick contiguous sections and should be processed for bone detail. Interference from fillings or other dental appliances can be avoided because the gantry can be angled to miss most of these objects; deeper implants and root canal pins can significantly degrade the study. Sections should be made parallel to the body of the mandible so as to avoid the anatomic confusion that occurs from sections made oblique to this plane. This is an important technical detail often omitted by radiologists unfamiliar with the study of cancers in this region. Recently, sophisticated computer software has become available that allows multiplanar reconstruction of CT data so that sections may be made radially around the entire course of the mandible (Fig. 16-17).[37] This technique can allow for precise evaluation of the bone stock available for reconstructive mandibular surgery. It also improves the precision in evaluating the extent of lesions relative to the inferior alveolar canal. These programs can reconstruct the data and produce sectional images through the mandible in a presentation similar to that seen on orthopantography.

The mandible may also be evaluated with radionuclide studies. A negative bone scan is useful in excluding mandibular invasion; however, positive studies are frequently falsely predictive of bone invasion. MRI is of

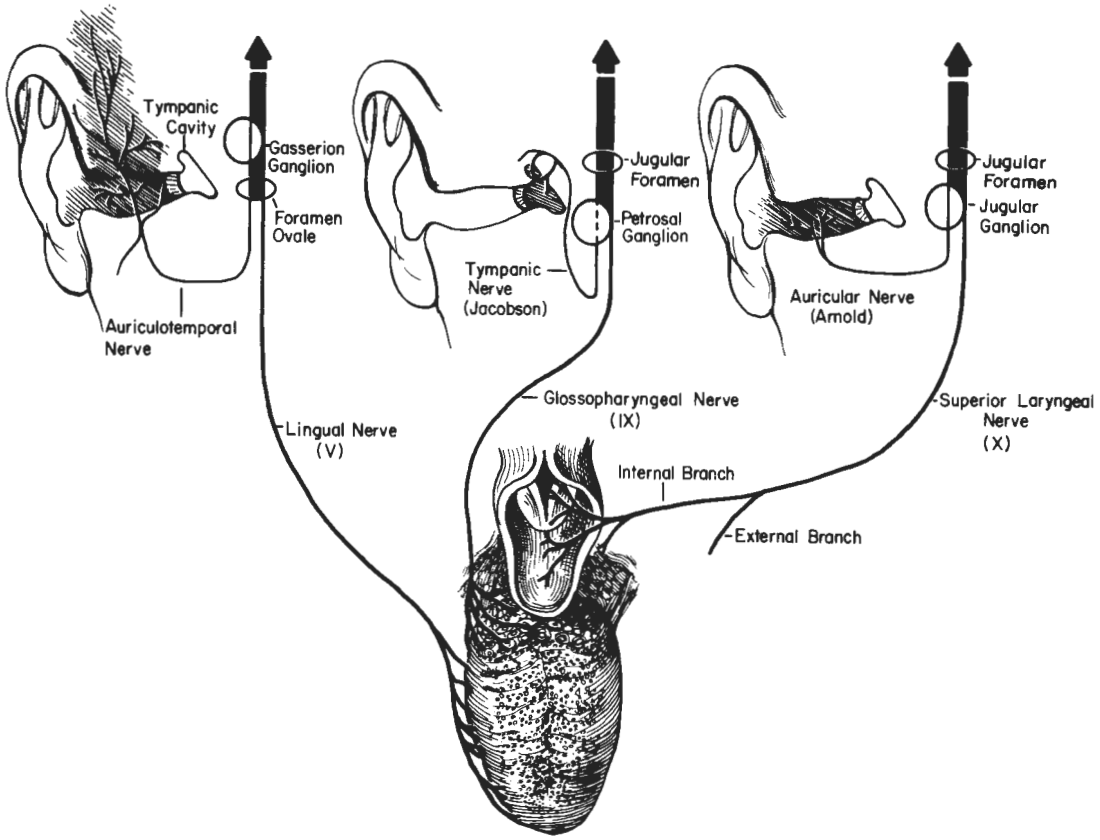


Figure 16-16. Pathways for referred pain to the ear. The auriculotemporal nerve (*left*) supplies the skin covering the front of the helix and tragus, the skin of the anterior wall of the external auditory canal, the tympanic membrane, and the skin of the temple. The tympanic nerve of Jacobson (*center*) supplies the tympanic cavity and produces a constant, deep-seated earache. The auricular nerve (*right*) is sensory to the skin of the back of the pinna and posterior wall of the external auditory canal. (Million RR, Cassisi NJ, Wittes RE. Cancer in the head and neck. In: DeVita VT Jr, Hellman S, Rosenberg SA, eds. Cancer: principles and practice of oncology, ed 2. Philadelphia, JB Lippincott, 1985:438)

value in detecting the spread of tumor within the marrow space. In floor of the mouth cancer, there is always obvious bone destruction on CT when tumor is spreading within the marrow space of the mandible, and MRI is seldom necessary for detection of mandible involvement. In highly selected cases, MRI may be used to evaluate the extent of marrow space infiltration and proximal spread along the inferior alveolar and mandibular nerves. Routine use of MRI, as suggested by some authors, is not indicated and can add considerable cost.

CT and MRI may be used to study the extent of deeply infiltrating floor of the mouth cancers. CT is the primary examination used at the University of Florida. Imaging may demonstrate spread that has gone far beyond that apparent from inspection or bimanual palpation. The more aggressive varieties of floor of the mouth cancer seem to spread freely within the sublingual space and along the muscle bundles of the tongue in many directions (Fig. 16-18). General direction and patterns are as follows: (1) Medial spread across the midline, either directly across the genioglossus muscle and lingual septum or by way of the potential space between the genioglossus and geniohyoid muscles. The precise relationship of the gross tumor margin to the contralateral lingual neurovascular bundle can be determined. (2) Lateral spread, usually contained by the mylohyoid muscle. MRI, in particular, can be used to determine if the mylohyoid muscle is displaced or partially or completely infiltrated. (3) Posterior spread, usually within the sublingual space along the mylohyoid muscle and into the deep spaces of the upper neck. Early spread to the neck is often not palpable. (4) Inferior spread, usually within the sublingual space, but perhaps continuing along the mylohyoid and hyoglossus muscle, sometimes as far inferiorly as attachments of these muscles on the hyoid bone. In advanced cases, direct spread through these muscles into the soft tissues of the suprahyoid neck and submandibular space is detectable only on imaging studies. Posteroinferior spread can result in extensive involvement of the tongue base, which may only become palpable in its most advanced state. (5) Spread into the oral tongue from floor of the mouth cancer. Such spread may not be palpable or visible.

Both ulcerated and nonulcerated tumors of the floor of the mouth may be associated with considerable inflammatory response. Neither CT nor MRI is capable of distinguishing between tumor and related inflammatory change. It is our policy to assume that there are tumor cells present wherever structural pathology is present. In the floor of the mouth, obstruction or inflammation of

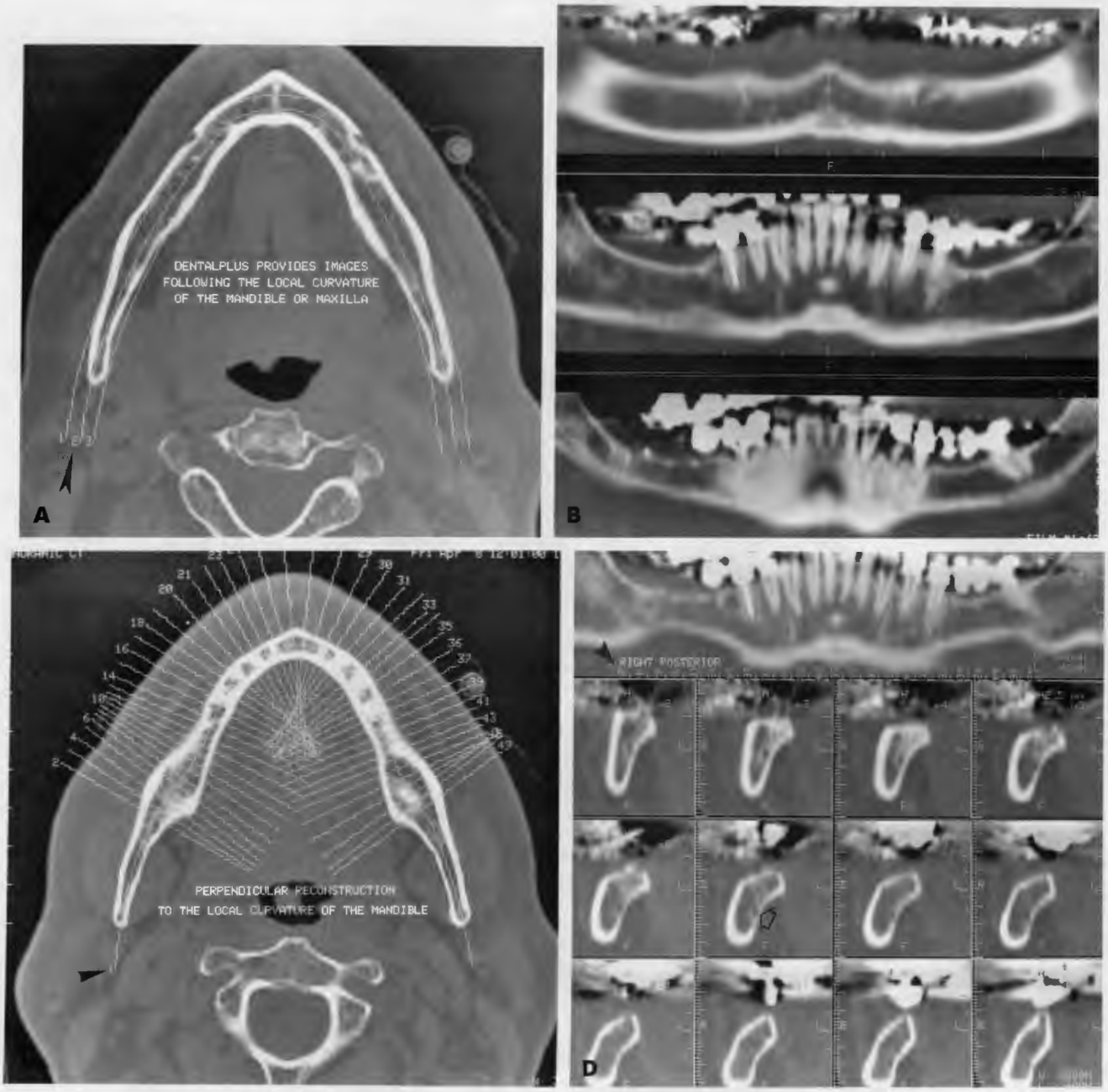


Figure 16-17. A set of contiguous 1.5- or 2-mm thick CT sections of the mandible or maxilla may be used to reformat images in planes other than standard sagittal and coronal sections. The required software is available from CT as well as independent vendors; the images here were created using a program called Denta-Plus (Dimensional Medicinal Imaging, Inc.). (*A*) A standard axial CT section made through the mid body of the mandible at about the level of the mental foramina. This is the single best view to survey the lingual and buccal surface of the mandible; however, reconstructed images may be used to evaluate the alveolar ridge and inferior margin of the mandible in a manner similar to panoramic radiography. The curved imaging planes labeled 1, 2, and 3 show how the curved, planar reconstructions through the mandible (*B*) are selected. (*C*) The software can also produce multiple images perpendicular to the plane of the lingual and buccal cortex of the mandible. The curved plane through the mandible labeled 1 (*arrowhead*) is first chosen. The computer calculates the position of images made along the curved plane as illustrated by the lines numbered 2 through 49. These generate a reference panoramic section (*D*), which has indexing numbers to show the position of each radially oriented section (*arrowhead*), some of which are shown in the set of 12 smaller images in *D*. Note the ability to evaluate the amount of bone stock along the alveolar ridge as well as the buccal and lingual surfaces of the mandible and the position of the inferior alveolar canal (*open arrow*). (Mancuso AA. Diagnostic imaging. In: Meyerhoff WL, Rice DH, eds. Otolaryngology—head and neck surgery. Philadelphia, WB Saunders, 1992:79)

the sublingual salivary glands may mimic tumor infiltration. Inflammation around an obstructed submandibular duct cannot be distinguished from periductal spread of tumor.

All patients with floor of the mouth cancer who come to imaging for evaluation of the primary site have a complete study of the regional nodes. Specific criteria for diagnosing positive lymph nodes are discussed in Chapter 6. There seems to be a particular tendency for small nodes in the submandibular region to undergo early capsular penetration; we have observed this in nodes as small as 5 mm in the submandibular group. The reason is unknown, and this represents an empiric observation. CT is useful in distinguishing between submandibular gland enlargement and enlarged submandibular nodes.

Staging

The AJCC staging given at the beginning of this chapter was developed for all oral cavity lesions. No specific consideration is given to tethering or fixation to the periosteum of the mandible. Fixation of the tongue, growth through the mylohyoid muscle to the skin in the submental area, or bone invasion qualify as T4.

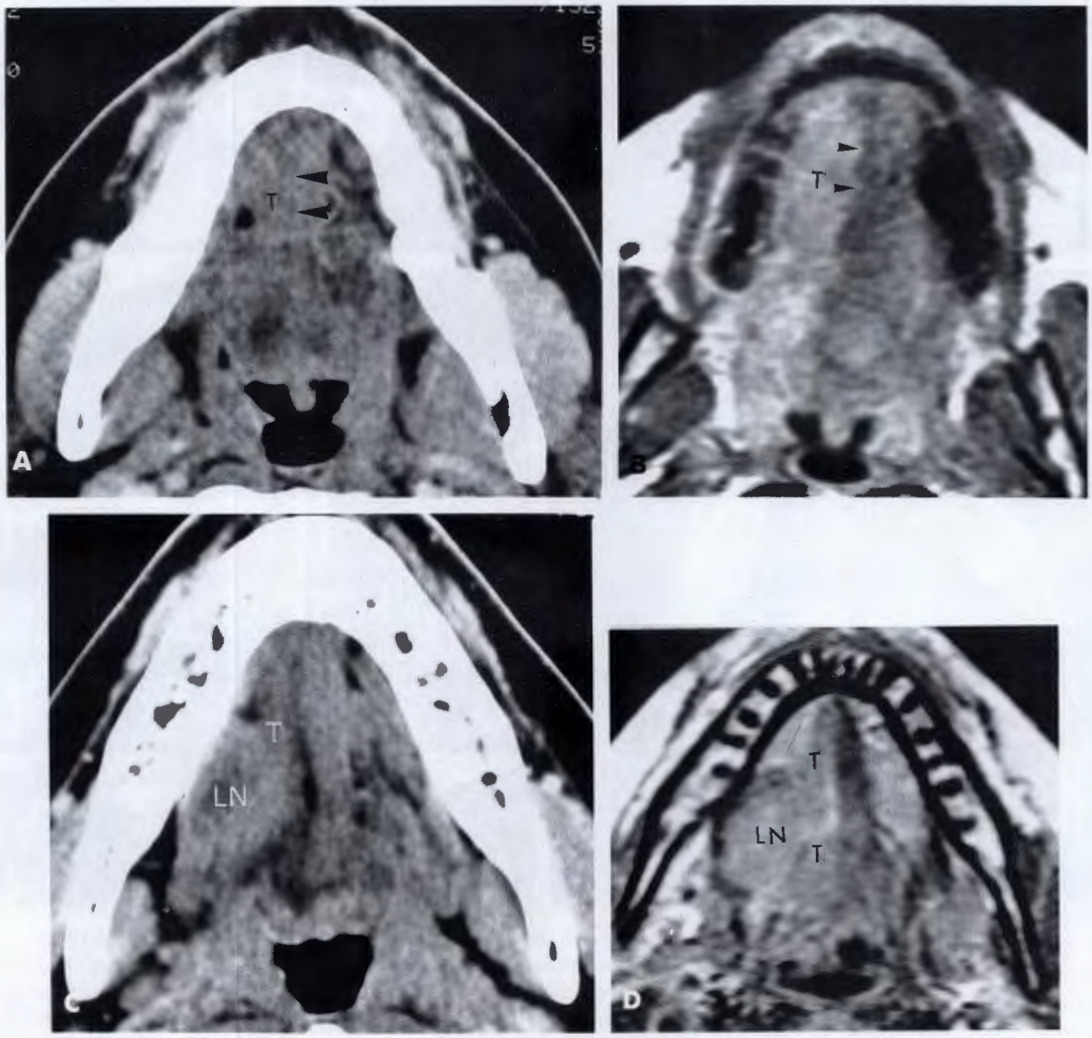


Figure 16-18. Patient with carcinoma of the oral tongue and floor of the mouth. (*A*) CT section through the oral tongue shows infiltrating tumor (T) obliterating the tissue planes within the oral tongue on the right side. The status of the midline (*arrowheads*) is uncertain. (*B*) MRI made at approximately the same level as in *A* shows that tumor (T) extends to but not across the midline (*arrowheads*). (*C*) CT section made through the floor of the mouth showing a more well-defined mass, possibly representing a lingual lymph node metastasis (LN), as well as the more medial component of the tumor (T) spreading within the sublingual space and genioglossus muscle. (*D*) MRI section at the same level as the CT section in *C*. The infiltration of the genioglossus muscle by tumor (T) is easier to appreciate and appears separate from the mass labeled LN. (*E* and *F*) Coronal, heavily T2-weighted MRI sections. (*E*) Image is made at approximately the level of the second bicuspid. Two components of the tumor are again visible. One is brighter and probably represents a lingual lymph node (LN). Note the invasion of the mylohyoid muscle (*arrowhead*) on the right side compared to the normal mylohyoid muscle (*open arrow on left*). (*F*) At approximately the level of the second or third molar, the primary tumor (T) and lingual lymph node (LN) are seen as separate masses. At this level, the mylohyoid muscle (*arrowhead*) is thinner compared to the opposite side, as a result of either invasion or stretching.

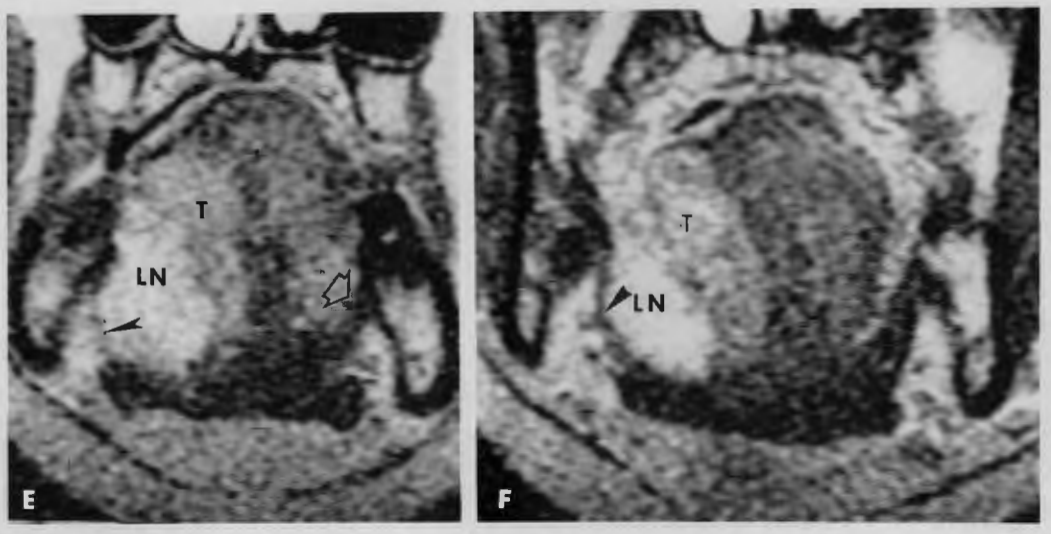


Figure 16-18. (*Continued*)

Treatment

Selection of Treatment Modality: Primary Site

LEUKOPLAKIA. Patches of thin leukoplakia are usually observed, and no biopsy or treatment is done. Biopsy is done if the area becomes symptomatic or if the appearance changes and malignancy is suggested. Localized areas of leukoplakia may be excised, but many patients have extensive or scattered areas that preclude complete excision. The carbon dioxide laser may be used for excision or evaporation of lesions. Isotretinoin (13-*cis*-retinoic acid), a synthetic retinoid, has been shown to suppress premalignant lesions of the oral cavity.[30] The drug has side effects of skin dryness, cheilitis, hypertriglyceridemia, and conjunctivitis. We have no experience with the drug.

Radiation therapy is not recommended for treatment of leukoplakia. When leukoplakia is inadvertently irradiated along with an adjacent carcinoma, the leukoplakia may disappear, but, in most cases, it will reappear at a later time.

EARLY LESIONS. Operation and radiation therapy produce similar cure rates for T1 and T2 lesions. The risk of radiation-induced bone and soft tissue necrosis is significant, and operation is usually selected except as outlined in the succeeding paragraphs.

A few patients are seen after excisional biopsy of a tiny lesion, and the only finding is a surgical scar with varying degrees of induration or nodularity under the scar (TX). The margins are stated to be free, close, or positive. If the excisional biopsy is judged to be inadequate, these patients are usually treated with an interstitial implant alone or an intraoral cone, because the surgeon has difficulty determining the extent of reexcision. The use of margin checks for reexcision is essentially useless under these conditions because few tumor cells are present and the pathologist is "looking for a needle in a haystack." Additionally, a few tumor cells may be spread at some distance from the excision site by way of the hematoma. The radiation therapist can be more generous with the treatment volume and cover potential spread without functional loss. The neck is usually observed. Six patients treated in this manner at M.D. Anderson Hospital[4] and seven similar patients treated at the University of Florida all had the disease locally controlled.[45] None of the patients developed neck nodes.

Small lesions, up to 5 mm in diameter, may be excised transorally if there is a margin of normal mucosa between the lesion and the gingiva. If the excision includes the submandibular duct, the submandibular gland and duct may be removed in continuity or the duct may be reimplanted.

A common presentation is an anterior midline lesion, 1 to 3 cm in diameter. Most of these lesions are managed by resection. If the lesion extends to the gingiva or is slightly adherent to the periosteum, the resection includes periosteum. If the lesion is firmly attached to the periosteum, a rim of mandible is included in the specimen (Figs. 16-19 and 16-20). Postoperative radiation therapy is advocated for positive margins. Preoperative radiation therapy is avoided because pathologic fracture or bone necrosis may develop after rim resection.

Radiation therapy may be selected for lesions that can be encompassed by an intraoral cone, because there is almost no risk of bone or soft tissue necrosis.

The less common lesions in the narrow lateral floor of the mouth fall into two general categories. One presentation involves the floor of the mouth and extends toward the mandible with little or no tongue invasion. These lesions are best managed by excision, including either a rim of mandible or mandibulectomy and neck dissection. A second presentation involves the floor of the mouth with extension toward the undersurface of the tongue. These lesions may be managed by resection or radiation therapy.

MODERATELY ADVANCED LESIONS. Nearly all of these lesions are tethered or fixed to the mandible or involve the adjacent gingiva. Rim resection, which preserves continuity of the mandible, produces a good cure rate with acceptable speech and swallowing and is the treatment of choice. Postoperative irradiation is added for close or positive margins, or for adverse findings in the neck. Preoperative irradiation is not advisable before rim resection. Success with irradiation varies widely, but the highest rate of local control occurs when interstitial irradiation or intraoral cone therapy is used as part of the treatment. The local control rate by T stage for three different radiation series is compared in Table 16-7.[16,26,50] The local control rates increase with increasing

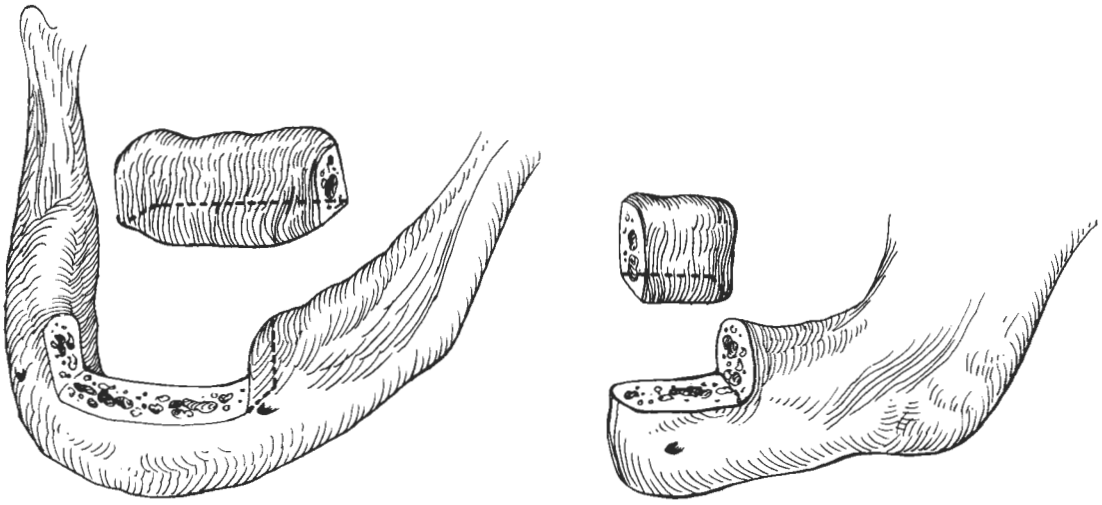


Figure 16-19. Schematic of rim resection for early carcinoma of the floor of the mouth. (Million RR, Cassisi NJ, Clark JR. Cancer of the head and neck. In: DeVita VT Jr, Hellman S, Rosenberg SA, eds. Cancer: principles and practice of oncology, ed 3. Philadelphia, JB Lippincott, 1989:509)

doses and a greater proportion of treatment given by interstitial implant; these high control rates are accompanied by a progressively higher risk of a complication. If the lesion can be encompassed by an intraoral cone in an edentulous patient, the risk of a serious complication is low.

Extension of tumor to the periosteum or gingiva does not preclude cure by radiation therapy. The results of treatment according to the degree of gingival or periosteal involvement for 25 T2 and T3 lesions are shown in Table 16-8. The control rate is 56% and independent of the extent of periosteal fixation; however, the incidence of minor and major complications in the patients with large, fixed lesions is high with interstitial therapy. If the operative alternative for a large, fixed lesion is a resection of the mandibular arch, floor of the mouth, and anterior tongue, which produces major disability even with reconstruction, radiation therapy may be selected as the initial treatment.

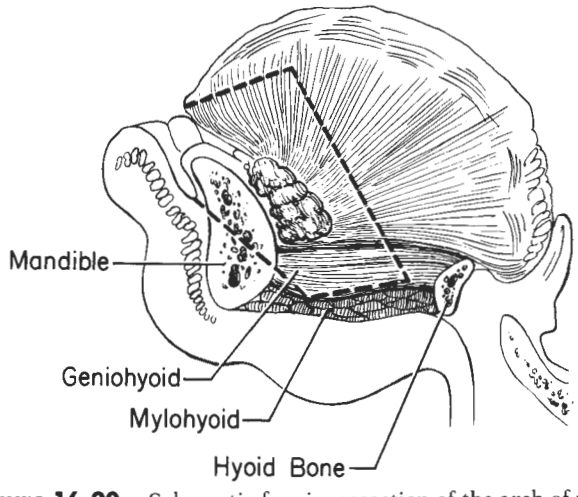


Figure 16-20. Schematic for rim resection of the arch of the mandible. (Million RR, Cassisi NJ, Clark JR. Cancer of the head and neck. In: DeVita VT Jr, Hellman S, Rosenberg SA, eds. Cancer: principles and practice of oncology, ed 3. Philadelphia, JB Lippincott, 1989:509)

ADVANCED LESIONS. Patients who have T4 lesions only because of bone invasion have a chance of cure with combined surgery and radiation therapy (Fig. 16-21). Only palliation can be offered to those who have extensive tongue invasion with fixation, extension to submental skin, or massive neck disease. Palliative treatment has usually been irradiation, two fractions of 1000 cGy delivered with a 7- to 10-day interval.

COMBINED TREATMENT POLICIES. The results of combined surgery and irradiation may be better than those for sequential therapy in the large, infiltrative, ulcerative lesions. Surgical resection with postoperative irradiation is preferred, but preoperative irradiation may be selected if the patient has a large fixed node. Advanced lesions that extend anteriorly to the skin of the lip are irradiated preoperatively to gain control of tumor in the dermal lymphatics and because the extensive reconstruction might delay the start of radiation therapy (see Fig. 16-21). If rim resection is possible, postoperative irradiation is preferred, because the risk of pathologic fracture, bone necrosis, and fistulas is higher with preoperative irradiation. Surgical clearance is most difficult in the tongue, and preoperative irradiation further obscures the borders of the disease. Postoperative irradiation portals often include the entire oral tongue and the floor of the mouth. The daily dose is 180 cGy, and the tumor dose is 6500 cGy. If the tongue margins are close or positive, the dose may be 7000 cGy. The acute side effects of this therapy are debilitating and painful.

Management of the Neck

See Chapter 6 for an overview of neck treatment.

PRIMARY LESION TREATED BY SURGERY

Clinically Negative Neck. The neck may be observed for superficially invasive stage I and II lesions if the pa-

TABLE 16-7. Carcinoma of the Floor of the Mouth: Local Control With Primary Radiation Therapy

		Stage T1		Stage T2		Stage T3		
Institution	Technique	RT Alone	Ultimate Control	RT Alone	Ultimate Control	RT Alone	Surgical Salvage	Ultimate Control
MD Anderson[16]	Mixed	48/49 (98%)	100%	68/77 (88%)	93%	46/60 (73%)	11	95%
University of Florida*	Mixed	32/37 (86%)	86%	25/36 (69%)	91%	11/20 (55%)	2	65%
University of California (San Francisco)[26]	External beam	29/38 (76%)	90% (approx.)	21/39 (54%)	70% (approx.)	8/32 (25%)	3	41%

RT, radiation therapy; mixed, external beam irradiation and interstitial implant.

* Rodgers L. Personal communication, April 1990.

(Modified from Million RR, Cassisi NJ, Clark JR. Cancer of the head and neck. In: De Vita VT Jr, Hellman S, Rosenberg SA, eds. Cancer: principles and practice of oncology, ed 3. Philadelphia, JB Lippincott, 1989:510)

tient will be regularly examined at 4- to 8-week intervals for 2 to 3 years (see Table 16-6). Findings of invasion greater than 2 mm, poorly differentiated tumor, vascular space invasion, or a pattern of diffuse invasion along the deep borders of the neoplasm should all be considered in the decision for ipsilateral or bilateral elective neck dissection. A neck dissection that removes the submental, submandibular, and subdigastric lymph nodes is usually sufficient, but, in recent years, a complete functional neck dissection has usually been done. Postoperative irradiation is considered with extracapsular spread or more than two involved lymph nodes. Elective neck irradiation is not recommended as a planned treatment with excision of the primary tumor because it is necessary to irradiate most of the floor of the mouth, oral tongue, and major salivary glands to encompass adequately the lymph nodes at risk. However, if postoperative radiation therapy is planned because of adverse findings at the primary site, irradiation can be used to treat the neck electively.

Clinically Positive Neck. See Chapter 6 for guidelines.

PRIMARY LESION TREATED BY IRRADIATION

Clinically Negative Neck. The radiation oncologist does not have the histologic evidence available to the surgeon and must make a guess as to the risk for lymph node metastasis and the necessity for elective neck irradiation. The neck may be observed for small, superficial lesions, assuming regular examinations at 4- to 8-week intervals for 2 to 3 years. Elective neck irradiation is advocated for the remainder of cases.

Clinically Positive Neck. See Chapter 6 for guidelines. Approximately one third of the total radiation dose is given by intraoral cone or interstitial therapy to the primary, and, therefore, the neck dose is usually limited to 4500 to 5000 cGy. Therefore, clinically positive neck nodes are managed by neck dissection or small-field boost irradiation. Large or fixed nodes are managed by localized boost irradiation to the mass followed by neck dissection.

Surgical Treatment

WIDE LOCAL EXCISION. Small, superficial lesions may be excised transorally with a 1-cm margin; the defect may be closed primarily or covered with a split-thickness skin graft. It may be necessary to remove adjacent periosteum to obtain a margin. If the duct is involved, the submandibular gland and duct are removed in continuity or the duct is reimplanted.

RIM RESECTION. Rim resection removes the mandible and periosteum adjacent to the tumor but does not remove the full thickness of the mandible and, therefore, leaves the bone intact while providing an adequate surgical margin (see Figs. 16-19 and 16-20). If the edge of the carcinoma is within 1 cm of the bone, rim resection should be considered. In some instances, only the periosteum is removed to provide the margin. The most common indication for the procedure is carcinoma either

TABLE 16-8. Carcinoma of the Floor of the Mouth: Local Control (Radiation Therapy Alone) Related to Gingival Extension (Stage T2-T3)

Extent of Disease	Local Control	Surgical Salvage	Ultimate Local Control	Complications Requiring Surgery
Minimal gingival/periosteal extension	4/8	3/4	7/8	1
Tethered to gingiva/periosteum	4/6	1/2	5/6	0
Fixed to gingiva	6/11	1/2	7/11	4
TOTAL	—	—	19/25 (76%)	—

Note: University of Florida data; patients treated October 1964 to December 1977; onalysis December 1979 by WM Mendenhall, MD.

Figure 16-21. (*A*) Advanced squamous cell carcinoma of the floor of the mouth with invasion of the tongue, gingiva, mandible, and skin of chin (1978). (*B*) Roentgenogram of mandible showing extensive bone destruction and penetration through the outer cortex. (*C*) Preoperative radiation therapy portals. Note bulging of skin of chin due to tumor in subcutaneous tissues. Skin was red and warm over the mass. The patient received 6000 cGy over 5 weeks, 120 cGy twice a day. The low neck received 5000 cGy over 5 weeks. (*D*) Appearance 6 months after bilateral hemimandibulectomy, resection of the floor of mouth, oral tongue, and adjacent soft tissues. Specimen was negative for tumor. Patient had no evidence of disease at 4½ years.

growing onto the gingiva or attached to the periosteum with normal radiographic studies.

The defect may be covered with a split-thickness skin graft in most unirradiated cases. If adequate floor of the mouth mucosa remains, the mandible may be covered with floor of the mouth mucosa and buccal or labial mucosa. A tongue flap is used when the lingual nerve has been sacrificed, because that portion of the tongue is numb and easily traumatized. The same flaps are used in the irradiated as in the unirradiated cases, but skin grafts have a lower rate of success; a flap may be necessary if the graft does not work.

Rim resection is most commonly employed for lesions in the anterior floor of the mouth, but it is also applied successfully to selected lesions in the lateral floor of the mouth.

Postoperative radiation therapy may be used after a rim resection that is repaired by a split-thickness graft.

Rim resection has been tried for four radiation therapy failures, but bone exposure and necrosis occurred in all four patients. Patients who have been edentulous for a long time may have a thin, atrophic mandible not suitable for rim resection because the mandible is likely to fracture.

Full or partial dentures may be used in most cases after rim resection.

MANDIBULECTOMY ("JAW-NECK"). The indications for mandibulectomy include imaging evidence of bone invasion, extensive deep infiltration of the floor of the mouth adjacent to the mandible, tumor growth into the dental sockets, and a thin mandible unsuitable for rim resection. A neck dissection is almost always added, because the neck is entered to perform the mandibulectomy.

Lateral Floor of the Mouth. A neck dissection is performed and the specimen remains attached to the mandible. Partial mandibulectomy with resection of the floor of mouth is done through a lip-splitting incision. A cheek flap is elevated to the level of the mandibular condyle to provide exposure. The mandible is separated at the mental foramen anteriorly and the neck of the condyle posteriorly. The primary lesion and neck specimen are removed in continuity. Primary closure is usually feasible, unless a sizable portion of the oral tongue must be removed, in which case a myocutaneous flap is necessary to repair the defect.

The cosmetic and functional result is acceptable to patients, and few request mandibular reconstruction. The mandible shifts to the opposite side, and if the patient has teeth, chewing may be impaired but may be corrected with a glide plane or mandibular reconstruction (see Chap. 9). Edentulous patients cannot wear a lower denture unless they have the mandible reconstructed and dental implants are used.

Anterior Floor of the Mouth. Lesions requiring full-thickness resection of the anterior mandible (arch) usually require removal from mental foramen to mental foramen. A spacer, such as a K wire or a cobalt–chromium alloy (Vitallium) tray, is necessary to maintain separation of the remaining mandible. This operation results in major cosmetic and functional loss and is usually reserved for advanced lesions with bone invasion or for irradiation failures (Fig. 16-22). (See Chap. 1 for the story of "Andy Gump.") New techniques for reconstruction include the use of a trapezius myocutaneous flap with a portion of the scapular spine to bridge the bony gap or a free flap such as iliac crest. Results are available for relatively few patients. These reconstructive efforts require extensive tissue dissection at the donor site and immobilization to promote healing. Moreover, there is still a significant failure rate of these flaps.

Figure 16-22. The "Andy Gump" appearance of a patient after resection of mandibular arch and floor of mouth before the modern era of reconstructive surgery.

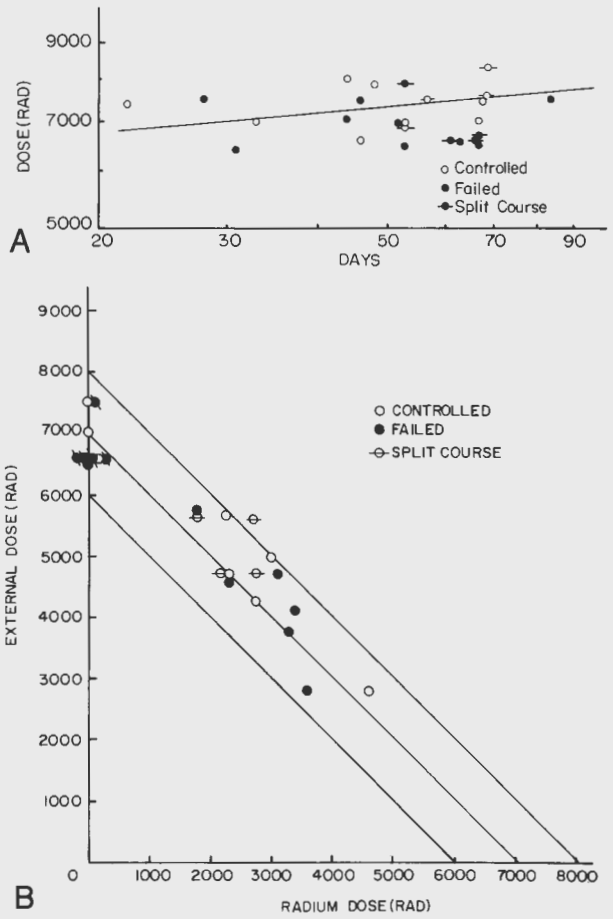


Figure 16-23. (*A*) T3 floor of mouth carcinoma: time–dose analysis. The interstitial dose is added to the external-beam irradiation dose. (*B*) T3 floor of mouth carcinoma: interstitial versus external-beam irradiation dose. (Mendenhall WM, Van-Cise WS, Bova FJ, Million RR. Analysis of time–dose factors in squamous cell carcinoma of the oral tongue and floor of mouth treated with radiation therapy alone. Int J Radiol Oncol Biol Phys 1981;7:1009)

Irradiation Technique

The availability of interstitial therapy and intraoral cone treatment is essential if maximum local control rates are to be obtained. External-beam irradiation alone gives inferior local control results even for T1N0 lesions (Tables 16-9 and 16-10).[16,26] Local control rate is related to total dose, the overall time, and the use of interstitial therapy or intraoral cone; the overall time does not seem to be as critical as it is for cancer of the oral tongue (Fig. 16-23).[47]

TABLE 16-9. Local Control of Lesions of the Oral Tongue and Floor of the Mouth as a Function of Radiation Modality Employed

	Oral Tongue			Floor of the Mouth		
Study	E + R vs E	R vs E	E + R vs R	E + R vs E	R vs E	E + R vs R
Chu and Fletcher[16]	E + R > E	R > E	No difference	E + R > E	R > E	No difference
Fu and coworkers[25]	—	—	No difference*	—	—	—
Fu and coworkers[27]	E + R > E	R > E	E + R < R†	—	—	—
Inoue and coworkers[32]	—	—	No difference	—	—	—
Horiuchi and Adachi[31]	E + R > E	R > E	E + R > R‡	—	—	—
Lees[33]	E + R > E	R > E	No difference	—	—	—
Mendenhall and coworkers[47]	—	—	E + R < R§	E + R > E#	—	No difference

E = external beam; R = radium.

* External plus more than 4000 cGy radium produced significantly better results than external plus less than 4000 cGy radium.

† Local control alone not reported by T stage.

‡ Difference noted primarily in T3 and T4.

§ T2 lesions

\# T3 lesions.

(Mendenhall WM, Van Cise WS, Bova FJ, Million RR. Analysis of time–dose factors in squamous cell carcinoma of the oral tongue and floor of mouth treated with radiation therapy alone. Int J Radiat Oncol Biol Phys 1981;7:1006)

The dose schemes prescribed at the University of Florida are shown in Table 16-11. Doses are based more on volume of tumor rather than diameter or T stage. A lesion may be 5 cm in total length and be superficial and more easily cured, whereas a lesion 2 to 3 cm in length may be 2 to 3 cm thick and invade the tongue and require higher doses.

INTRAORAL CONE AND INTERSTITIAL IRRADIATION. Intraoral cone is preferred to interstitial therapy when technically feasible. The major advantages are less dose to the adjacent bone and avoidance of an implant. An intraoral cone is best suited for anterior lesions in the edentulous patient. Lesions up to approximately 2 cm thick are suitable for intraoral cone therapy. The orthovoltage cones in use at the University of Florida are 2 to 6 cm in diameter; they are poured from lead and can be individually trimmed to adapt the cone to the anatomy (see Chap. 14). Intraoral cone therapy requires careful daily positioning by the physician.

The cone therapy is done first to avoid a sore mouth and to clearly see the lesion through the periscope. A pin is placed in the posterior border of the lesion for reference on the simulator film for external beam planning. The daily dose is 275 to 300 cGy with 250 kV, 0.5-Cu filter, to 1500 to 2400 cGy. The intraoral cone therapy is followed immediately by 5000 cGy over 5 weeks by external beam. Small superficial lesions may be treated with intraoral cone alone, 4500 cGy in 15 fractions over 3 weeks.

The edentulous patient is most suitable for intraoral cone therapy because the mandible atrophies with time and placement of the cone is relatively easy. If teeth are present, a few may have to be removed to obtain satisfactory cone placement. The teeth would have to be removed in any event for rim resection or interstitial implant. The risk of bone necrosis is almost nil.

Lesions with extension to the mucosa of the tongue, minimal extension to the gingiva, or tethering to the periosteum can sometimes be encompassed with a cone, but may be better managed by interstitial irradiation in conjunction with external-beam irradiation.

It has been customary to complete the external-beam therapy before the implant. However, the implant would often be easier to perform before the external-beam therapy, while the lesion is easily outlined and the patient is free of the acute side effects of external-beam treatment.

TABLE 16-10. Carcinoma of the Floor of the Mouth: Local Control Versus Proportion of Dose Delivered by Radium Implant

Stage	Radium or Radium Plus <3000 cGy	Radium Plus ≥3000 cGy	External Beam
T1	8/8	4/5	2/3
T2	1/1	9/12	3/4
T3	1/2	8/13*	3/10*
T4	n.d.	1/3	n.d.

n.d., no data.

* Significance level = .11, Fisher's exact test.

(Modified from Mendenhall WM, Van Cise WS, Bova FJ, Million RR. Analysis of time–dose factors in squamous cell carcinoma of the oral tongue and floor of mouth treated with radiation therapy alone. Int J Radiat Oncol Biol Phys 1981;7:1008)

TABLE 16-11. Carcinoma of the Floor of Mouth: Dose Schemes Currently Prescribed at the University of Florida

	Interstitial Only (cGy)	Intraoral Cone Only (cGy)	External Beam Plus Interstitial (cGy)	Intraoral Cone Plus External Beam (cGy)
TX—No visible or palpalable tumor	5500	4500 over 3 wk	Not recommended	Not recommended
TX—Palpable induration or positive margin	6500	5500 over 4 wk	4500 plus 2500	1500–1800 in 10 fractions plus 5000
Early, superficial	6000–6500	4500 over 3 wk	Not recommended	Not recommended
Early, 1–3 cm, induration	Not recommended	Not recommended	4500 plus 2500	1500–2400 in 10 fractions plus 4500
Moderately advanced (3–5 cm, induration)	Not recommended	Not recommended	4500 plus 3000	Not recommended
Advanced	Not recommended	Not recommended	7440–7680 (120 twice a day)	Not recommended

(Million RR, Cassisi NJ, Clark JR. Cancer of the head and neck. In: DeVita VT, Hellman S, Rosenberg SA, eds. Cancer: principles and practice of oncology, ed 3. Philadelphia, JB Lippincott, 1989:510)

A preloaded, custom-designed, metal or plastic implant device for radium or cesium needles has been in use at the University of Florida since 1976.[40] It holds the needles in a fixed position. The location of the needles relative to the gingiva can be tailored. Homogeneity of dose is improved because the implant design is checked by computer calculations before implantation. This device avoids piercing and unnecessarily irradiating the tongue, as was required with freehand needle techniques. The entire implant is completed in an instant with minimal exposure and minimal implant trauma. The custom holder is suitable only for T1 and T2 lesions. The arrangement of the needles for early lesions is usually a modified, curved, teardrop-shaped, two-plane implant with a single needle crossing the top of the implant (Fig. 16-24). The use of the implant holder for an early lesion of the floor of mouth is shown in Figure 16-25.

Implants for late T2 and T3 lesions are usually modified volume or multiplane arrangements. Radium or cesium needles or ^{192}Ir hairpins are inserted through the tongue. Sources at least 4.0 to 4.5 cm in active length are required.

When irradiation is planned after excisional biopsy, if the margins of the excisional biopsy are free or close and there is little or no induration or nodularity, 5000 to 5500 cGy is delivered by implant or 4500 cGy over 3 weeks by intraoral cone. If the margins are positive or if there is slight induration or nodularity, the implant dose is raised to 6000 to 6500 cGy and the cone dose is increased to 5500 cGy over 4 weeks. In cases where gross cut-through is suspected, one may wish to use external-beam irradiation, 4500 cGy, to include regional nodes before the interstitial implant or intraoral cone therapy.

EXTERNAL-BEAM IRRADIATION. External-beam portals for carcinoma of the anterior floor of the mouth are usually opposed lateral portals. The tongue is positioned by use of rubber corks taped to a wooden tongue blade (Figs. 16-26 and 16-27).[59] If the lesion is small and confined to the floor of the mouth, the tip of the tongue is elevated out of the portal and the lip is pressed outward. The dotted lines in Figure 16-26 show the borders of the portal. If the lesion has grown into the tongue, the tongue is depressed or flattened to reduce the superior border. The entire width of the arch of the mandible is

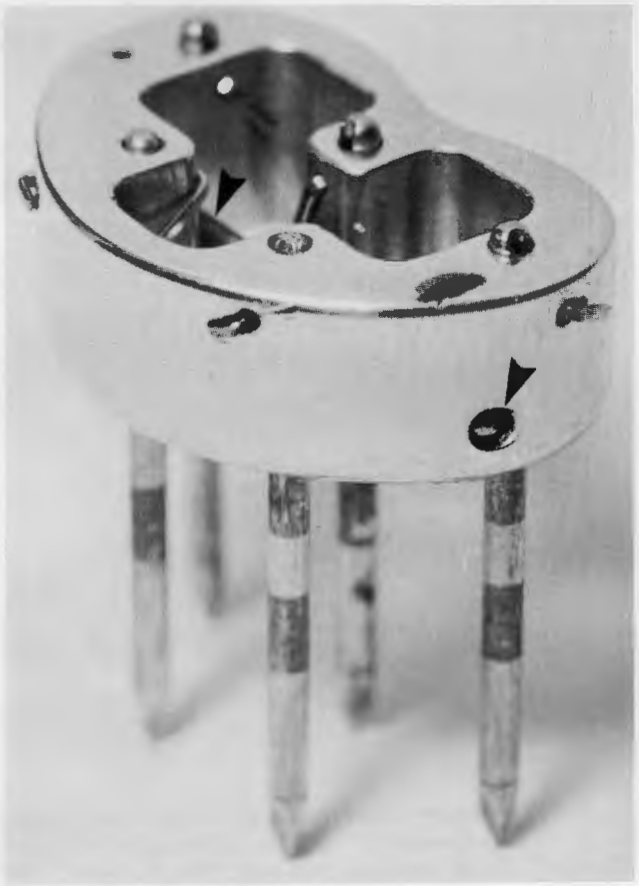


Figure 16-24. Custom-made implant device for stage T1-T2 carcinomas of the floor of the mouth. Note single crossing needle through center of device (*arrowheads*). The device is now machined from nylon. Cesium needles have replaced the radium needles. (Modified with permission from Marcus RB Jr, Million RR, Mitchell TP. A preloaded, custom-designed implantation device for stage T1-T2 carcinoma of the floor of the mouth. Int J Radiat Oncol Biol Phys 1980;6:112)

included in the portal. The superior border is shaped when the neck is clinically negative to spare part of the oral cavity, parotid, and minor salivary glands (Fig. 16-28). If the neck is clinically involved, the portal is enlarged, but the lower border remains near the thyroid notch. A stainless-steel pin is inserted into the posterior border of the tumor as a marker for external-beam therapy and for confirmation of coverage at the time of implant. The submental, submandibular, and subdigastric nodes are included to the level of the thyroid notch if the neck is clinically negative; the risk of subclinical disease in the lower neck is small, and the addition of an anterior

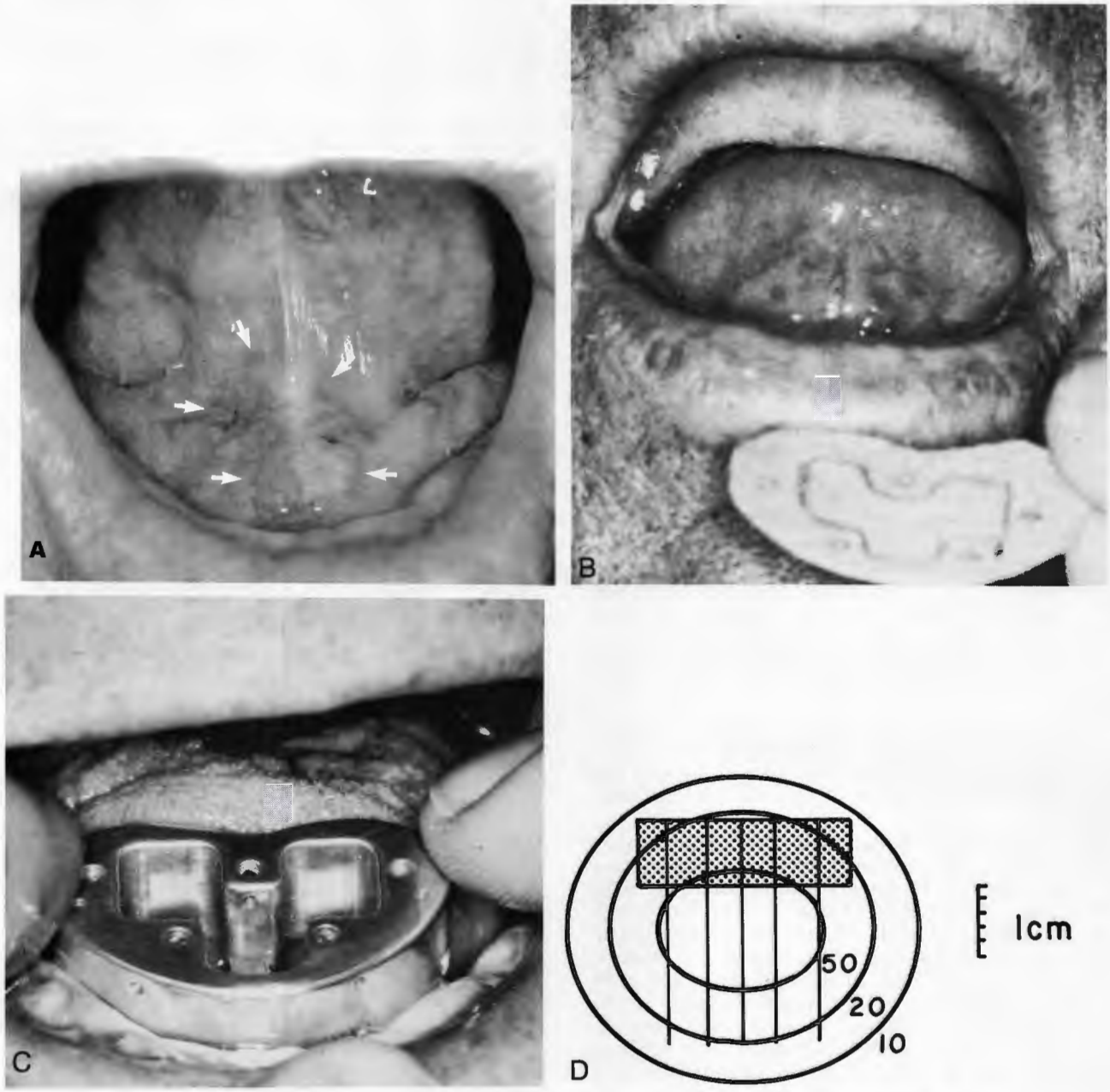
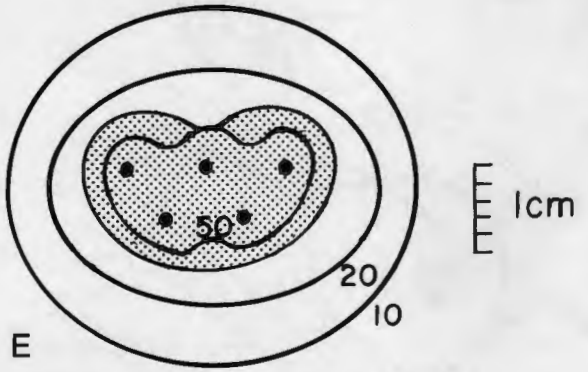


Figure 16-25. (*A*) Squamous cell carcinoma of the floor of the mouth (T2N0) (*arrows*). The lesion measured 2.5 × 2.5 cm, including the induration, and was tethered to the periosteum in the midline. The treatment plan was 5000 cGy over 5 weeks with parallel opposed portals that included the submaxillary and subdigastric lymph nodes. The midjugular lymph nodes were treated with an anterior portal. An implant was planned to add 1500 cGy. (*B*) Cardboard template used for design of the radium needle holder. (*C*) Implant in position. Device was secured with two sutures from the submental skin. There were five, 2.0-cm active length, full-intensity needles without crossing. (*D*) Sagittal isodose distribution. The 50-cGy-per-hour line was selected for specification at dose, and the implant remained in place for 30 hours. Stippled area represents the implant device. (*E*) Midplane isodose distribution. The 50-cGy-per-hour isodose line is approximately 1 mm outside the needles. The highest dose rate to the anterior lingual gingiva would be about 30 to 35 cGy per hour or at least 450 cGy lower than the minimum tumor dose. (*F*) The patient was free of disease at 4 years with no complications.



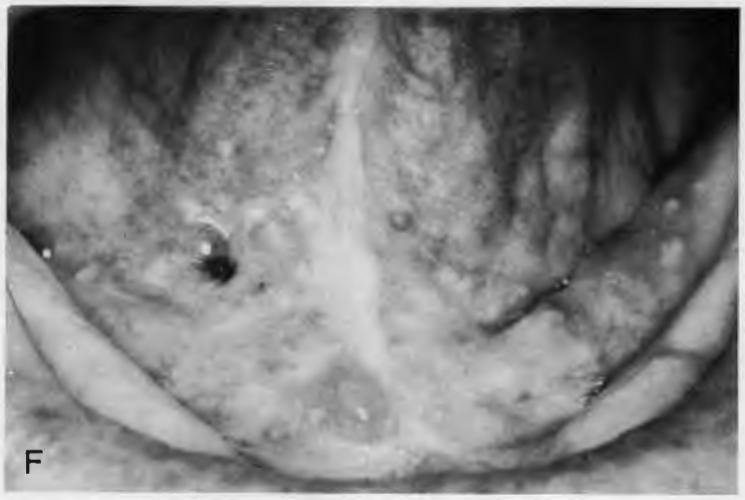


Figure 16-25. (*Continued*)

low-neck portal is individualized. The submental nodes are included coincidentally, although they are uncommonly involved. Note the sparing of about 1 cm of skin and subcutaneous tissue in the submental area. If the neck is clinically positive, the portals are enlarged to include all of the upper neck nodes, and an en face lower neck field is added.

For postoperative irradiation, lateral portals are used that include the primary site and upper neck nodes to the level of the thyroid notch. The lower neck is treated through a separate anterior portal with a larynx shield. (See Chaps. 5 and 12 for a discussion of dose in the postoperative setting.)

Management of Recurrence

Radiation therapy failure is treated by an operation. The salvage rate is high for patients with early lesions and moderately good for the more advanced lesions (see Table 16-7). Rim resection may be tried for radiation therapy failure, but the risk of complications is high in our limited experience.

Surgical failure may be treated by a repeat operation, radiation therapy, or both on an individual basis. Radiation therapy is not likely to salvage patients after surgical failure except in the case of a limited recurrence that can be implanted as part of the treatment. (See Chapter 6 regarding management of neck recurrence.)

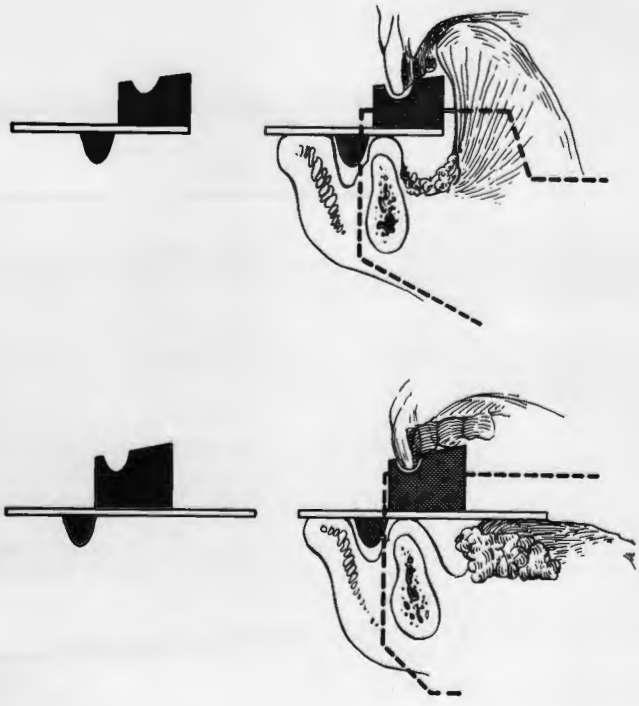
Results of Treatment

Rodgers and associates[65] reviewed 194 patients treated at the University of Florida between October 1964 and December 1987. The primary lesion was usually managed by radiation therapy in the early years of the study. Surgery or combined therapy gradually replaced radiation therapy during the past 10 years when rim resection became a surgical option. Rates of local control, total control above the clavicles, and 5-year cause-specific survival are detailed in Tables 16-12 through 16-14. Patients treated with split-course technique are included in the irradiation group. The treatment results for a subgroup of 34 evaluable patients with floor of mouth carcinomas managed by rim resection are shown in Tables 16-15 through 16-17.

Guillamondegui and Jesse[29] reported 20 patients treated by rim resection. All patients had invasion of the periosteum, and seven had early bone invasion on pathologic examination of the specimen. With 1-year minimum follow-up, there was only one local recurrence. Four patients had recurrence in the neck, however, and, for this reason, the authors recommend postoperative radiation therapy.

Beecroft and associates[8] reported the results for 34 patients (29 T1 or T2) managed by marginal mandibular rim resection with or without neck dissections; 11 patients had tumor approximating the mandible without gross tumor invading bone. There was one local recurrence salvaged by radiation therapy. The 5-year cause-specific survival rate was 81%; four patients died of cancer.

(*text continues on page 356*)



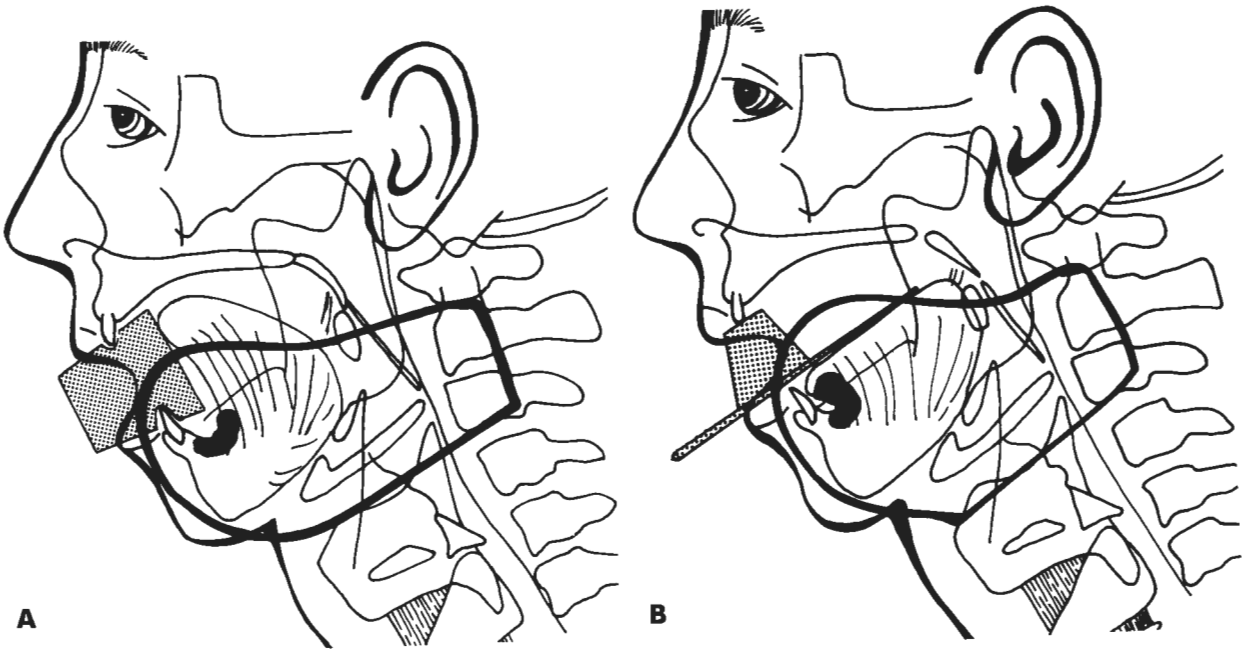


Figure 16-27. (*A*) Portal for treatment of carcinoma of the floor of the mouth with tongue invasion; the tongue is depressed into the floor of the mouth with a tongue blade and cork. (*B*) Portal for irradiation of limited anterior floor of mouth carcinoma without tongue invasion. Two notches are cut on a cork so that it can be held in the same position between the patient's upper and lower incisors during every treatment session; the tip of the tongue is displaced from the treatment field. The anterior border of the field covers the full thickness of the mandibular arch. The lower field edge is at the thyroid cartilage, ensuring adequate coverage of the submandibular lymph nodes. The subdigastric lymph nodes will be adequately covered by treating the entire width of the vertebral bodies posteriorly or 1 cm behind the posterior border of the sternocleidomastoid muscle. The superior border is shaped so that much of the oral cavity, oropharynx, and parotid glands are out of the portal. The minimum tumor dose is specified at the primary site (ie, not along the central axis of the portal) with the aid of computer dosimetry. (Parsons JT, Million RR. Radiation therapy of tumors of the oral cavity. In: Thawley SE, Panje WR, eds. Comprehensive management of head and neck tumors, vol 1. Philadelphia, WB Saunders, 1987:522, 523)

TABLE 16-12. Initial and Ultimate Local Control*

T Stage	Radiation Therapy Alone	Surgery Alone	Surgery and Radiation Therapy
T1			
Initial	32/37 (86%)	9/10 (90%)	1/1 (100%)
Ultimate	35/37 (94%)	9/10 (90%)	1/1 (100%)
T2			
Initial	25/36 (69%)	9/12 (75%)	7/7 (100%)
Ultimate	31/36 (86%)	10/12 (83%)	7/7 (100%)
T3			
Initial	11/20 (55%)	†	9/9 (100%)
Ultimate	13/20 (65%)	†	9/9 (100%)
T4			
Initial	2/5 (40%)	1/2 (50%)	5/8 (63%)
Ultimate	2/5 (40%)	1/2 (50%)	5/8 (63%)

* Grouped by initial treatment to the primary site. Forty-seven patients were excluded from local control analysis becuase they died within 2 years of treatment with the primary site continuously disease-free.
† No patients in category.
(Rodgers LW Jr, Stringer SP, Mendenhall WM, Parsons JT, Cassisi NJ, Million RR. Management of squamous cell carcinoma of the floor of the mouth. Head Neck 1993;15:17)

TABLE 16-13. Initial and Ultimate Control Above Clavicles*

Stage	Radiation Therapy Alone	Surgery Alone	Surgery and Radiation Therapy
I			
Initial	28/35 (80%)	8/10 (80%)	0/1 (0%)
Ultimate	33/35 (94%)	9/10 (90%)	0/1 (0%)
II			
Initial	17/26 (65%)	5/7 (71%)	4/5 (80%)
Ultimate	20/26 (77%)	6/7 (86%)	4/5 (80%)
III			
Initial	14/23 (61%)	2/3 (67%)	8/10 (80%)
Ultimate	18/23 (78%)	3/3 (100%)	8/10 (80%)
IVA			
Initial	3/11 (27%)	0/1 (0%)	3/4 (75%)
Ultimate	5/11 (45%)	0/1 (0%)	3/4 (75%)
IVB			
Initial	2/6 (33%)	0/4 (0%)	5/9 (56%)
Ultimate	2/6 (33%)	0/4 (0%)	5/9 (56%)

* Grouped by initial treatment to the primary site. Management of the neck varied and included no treatment, irradiation, neck dissection, or neck dissection and preoperative or postoperative irradiation. Thirty-nine patients were excluded from local–regional control analysis because they died within 2 years of treatment with the primary site and neck continuously disease-free.
(Rodgers LW Jr, Stringer SP, Mendenhall WM, Parsons JT, Cassisi NJ, Million RR. Management of squamous cell carcinoma of the floor of the mouth. Head Neck 1993;15:18)

TABLE 16-14. Carcinoma of the Floor of the Mouth: 5-Year Cause-Specific Survival Rate—194 Patients

Stage	Radiation Therapy Alone	Surgery Alone	Surgery and Radiation Therapy
I	22/23 (96%)	4/6	No data
II	14/20 (70%)	5/6	No data
III	14/21 (67%)	2/3	5/8
IVA	4/9	0/1	1/3
IVB	1/5	1/4	2/8

(Modified from Rodgers LW Jr, Stringer SP, Mendenhall WM, Parsons JT, Cassisi NJ, Million RR. Management of squamous cell carcinoma of the floor of the mouth. Head Neck 1993;15:19)

TABLE 16-15. Carcinoma of the Floor of the Mouth Treated With Rim Resection: Local Control After Initial Treatment—28 Patients*

Stage	Surgery Alone	Surgery and Radiation Therapy
T1	3/4	No data
T2	8/11†	5/5
T3	No data	4/4
T4	1/1	2/3

* Six patients excluded from analysis of local control.
† One patient salvaged with further treatment.
Note: University of Florida data; patients treated October 1964 to December 1987; analysis December 1989 by L Rodgers, MD.

TABLE 16-16. Carcinoma of the Floor of the Mouth Treated With Rim Resection: Ultimate Control Above the Clavicles—34 Patients

Stage	Surgery Alone	Surgery and Radiation Therapy
I	3/4 (75%)	1/2 (50%)
II	5/5 (100%)	3/4 (75%)
III	2/2 (100%)	5/6 (83%)
IVA	1/2 (50%)	2/2 (100%)
IVB	1/2 (50%)	2/5 (40%)

Note: University of Florida data; patients treated October 1964 to December 1987; analysis December 1989 by L Rodgers, MD.

TABLE 16-17. Carcinoma of the Floor of the Mouth Treated With Rim Resection: 5-Year Cause-Specific Survival

Stage	Surgery Alone	Surgery and Radiation Therapy
I	2/3	No data
II	3/3	0/1
III	0/1	2/4
IVA	0/1	No data
IVB	0/2	1/5

Note: University of Florida data; patients treated October 1964 to December 1987; analysis December 1989 by L Rodgers, MD.

Follow-Up Policy

Patients are seen at 4- to 8-week intervals for the first 2 years, every 3 to 4 months for the third year, and then every 6 months.

There are two major diagnostic difficulties in follow-up after irradiation: soft tissue ulcer and enlarged submandibular gland. A bone exposure is almost always a necrosis and not due to cancer.

The appearance of an ulcer in the floor of the mouth within 2 years of irradiation can represent either recurrence or necrosis. If the lesion appears to be a soft tissue necrosis, a trial of conservative therapy and observation at close intervals is adequate. The soft tissue necroses are notoriously slow to heal. Failure to stabilize or show some indication of healing is an indication for biopsy. A negative biopsy does not rule out recurrence, and if the lesion remains suspicious, repeat deep biopsies are in order.

The benefits and limitations of imaging in detecting recurrence are discussed in Chapter 4. Enlargement of the submandibular glands is a common sequel to obstruction of the submandibular duct. CT or MRI may be helpful in these situations. Either may clearly show a metastatic node as the explanation. Alternatively, the imaging study may show the submandibular gland to be enlarged due to sialadenitis or obstruction. If the submandibular ducts have been reimplanted, obstruction may develop with submandibular gland enlargement; metastatic cancer to the submandibular gland must be excluded (see Fig. 6-29). If, after imaging, it is still difficult to distinguish between an enlarged submandibular gland and tumor in a lymph node or submandibular gland, only removal clarifies the situation. A negative needle biopsy is helpful but not entirely reliable.

Large split-thickness skin grafts and flaps increase the difficulty in distinguishing normal scar from recurrent tumor.

Complications of Treatment

Radiation Complications

A small soft tissue necrosis may develop in the floor of the mouth, usually at the site of the original lesion where the dose is highest. These ulcers are moderately painful and respond to local anesthesia, antibiotics, and time. A decision regarding biopsy depends on the clinical course.

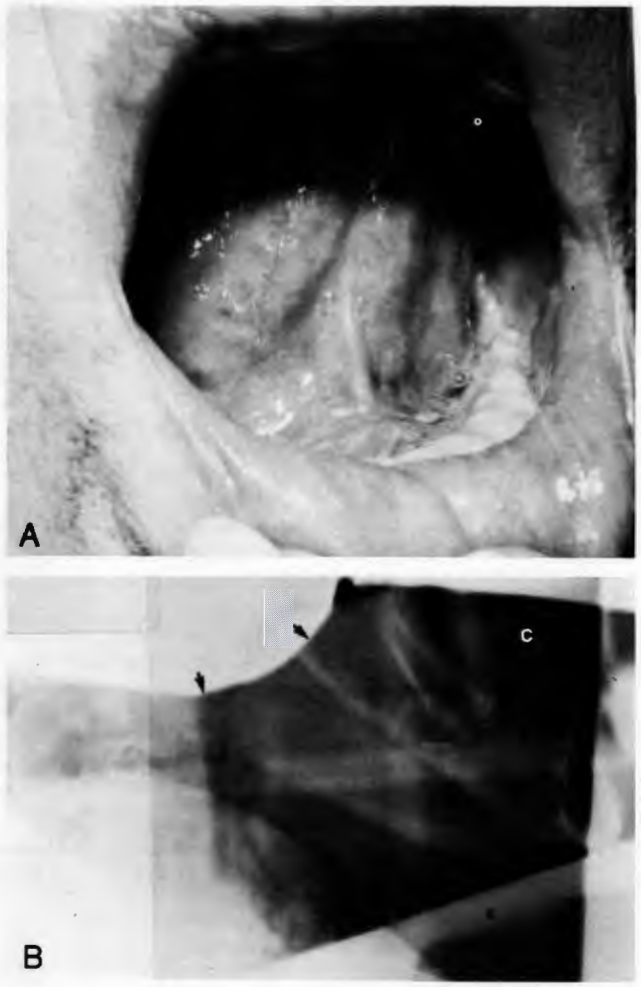


Figure 16-28. (*A*) A 55-year-old woman presented with a 2.2 × 1.0-cm squamous cell carcinoma in the left anterior floor of the mouth that was slightly tethered to the periosteum; most of the lesion was submucosal. The lesion extended to the midline. The roentgenographic appearance of the mandible was normal. The lower teeth showed marked periodontal disease. The neck was negative (T2N0). The patient was offered surgery or radiation therapy and elected irradiation. The remaining teeth were extracted before start of treatment. (*B*) Roentgenogram of external-beam portal. Stainless-steel pin represents posterior border of lesion. A cork (c) displaces the tip of the tongue superiorly. The superior margin of portal (*arrows*) is shaped to spare part of the parotid and other normal structures. The posterior border encompasses the spinal canal and could be slightly less. Approximately 1 cm of submental skin and subcutaneous tissues is shielded (X). The tumor dose was 5000 cGy over 5 weeks to the floor of the mouth and lymph nodes. (*C*) Radium needle implant for 2000-cGy tumor dose. (*D*) The mucosa healed initially, but a 7-mm area of bone exposure developed at 7 months. (*E*) At 1 year, bone exposure persisted. Symptoms were mild and intermittent. The exposed bone was smoothed with a file; 3 months later, the gingiva appeared nearly healed. (*F*) Three small areas of bone exposure are shown at 2 years. (*G*) At 2½ years, a 5-mm area of bone exposure appeared; it was associated with a small abscess that extended lateral to the mandible and seemed to communicate with the bone exposure. The abscess disappeared in 1 week with antibiotics. (*H*) No evidence of tumor at 5 years and no new necroses after 3½ years.

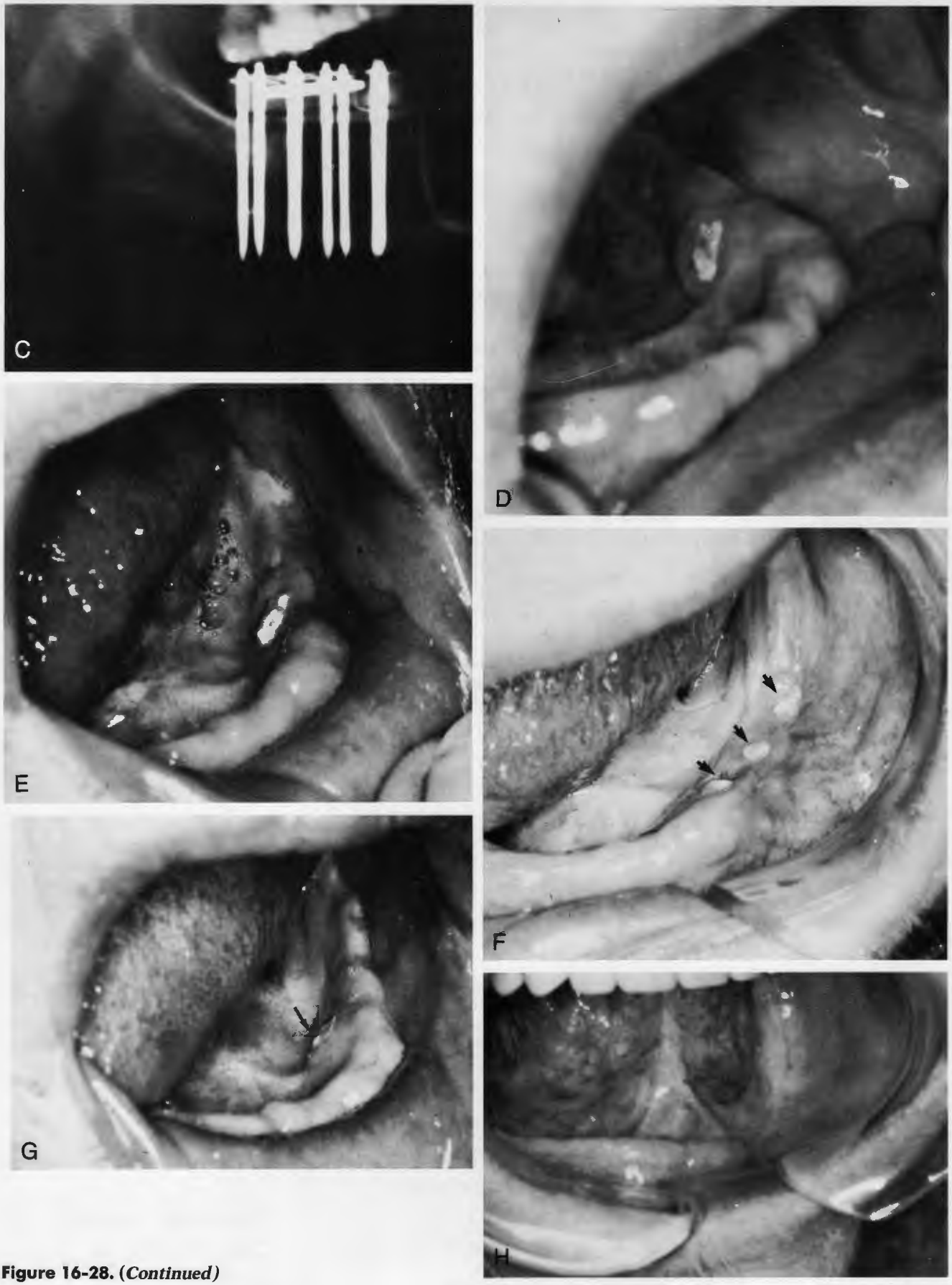


Figure 16-28. (*Continued*)

TABLE 16-18. Carcinoma of the Floor of the Mouth: Complications of Treatment—194 Patients

Initial Treatment	Patients With Severe* Complications	Patients With Mild to Moderate† Complications
Radiotherapy alone	6/117 (5%)	49/117 (42%)
Surgery alone	6/36 (17%)	3/36 (8%)
Surgery and radiotherapy (preoperative or postoperative)	6/41 (15%)	8/41 (20%)

* Postoperative complications (myocardial infarction, pulmonary embolism, and so forth), wound infection or dehiscence, fistula formation, or osteoradionecrosis requiring hospitalization or surgical intervention.
† Small bone exposure, soft tissue necrosis, or minor infection. Osteoradionecrosis or surgical wound complication requiring outpatient therapy only.
(Modified from Rodgers LW Jr, Stringer SP, Mendenhall WM, Parsons JT, Cassisi NJ, Million RR. Management of squamous cell carcinoma of the floor of the mouth. Head Neck 1993;15:18)

If the ulceration develops on the adjacent gingiva, the underlying mandible is exposed. These areas are mildly painful. They are managed by discontinuing dentures, applying a local anesthetic, administering antibiotics, and smoothing of the bone by filing if needed. These small bone exposures do not often progress to full-blown osteonecrosis. A small piece of bone may sequestrate, and the bone may be re-covered by mucous membrane. Healing is slow, and the patient requires constant reassurance that the discomfort and ulcer are not due to cancer. Hyperbaric oxygen and débridement may be added to the therapy if the necrosis is progressing (see Chap. 10 and the section on complications of radiation treatment of cancer of the oral tongue later in this chapter). The complications for 117 patients treated by radiation therapy and 41 patients treated by combined treatment are outlined in Table 16-18.[65] Resection of the mandible for necrosis occurred in six patients.

Surgical Complications

Surgical complications include wound infection, bone exposure, and orocutaneous fistula; orocutaneous fistula may lead to osteomyelitis and pathologic fracture. The complications for surgery alone and combined treatment at the University of Florida were detailed in Table 16-18.

Beecroft and coworkers[8] reported the complications for 34 patients undergoing marginal mandibulectomy. There was one operative mortality. Four patients developed a fistula, of which three progressed to osteomyelitis and fracture of the mandible requiring removal of the bony segment.

Fracture of the mandible after rim resection is uncommon. Salvage procedures after radiation therapy are associated with an increased risk of mandible complications. Removal of the oral tongue may produce a speech defect and difficulty in swallowing. Mandibulectomy of the arch is associated with oral incompetence and disfigurement.

ORAL TONGUE

Anatomy

The muscular anatomy of the tongue is shown in Figure 16-29.[17] The circumvallate papillae locate the division between oral tongue and base of tongue. The papillae foliatae are 2- to 4-mm, slightly elevated, irregular areas on the dorsum at the junction with the anterior tonsillar pillar. There are mucous and serous glands beneath the

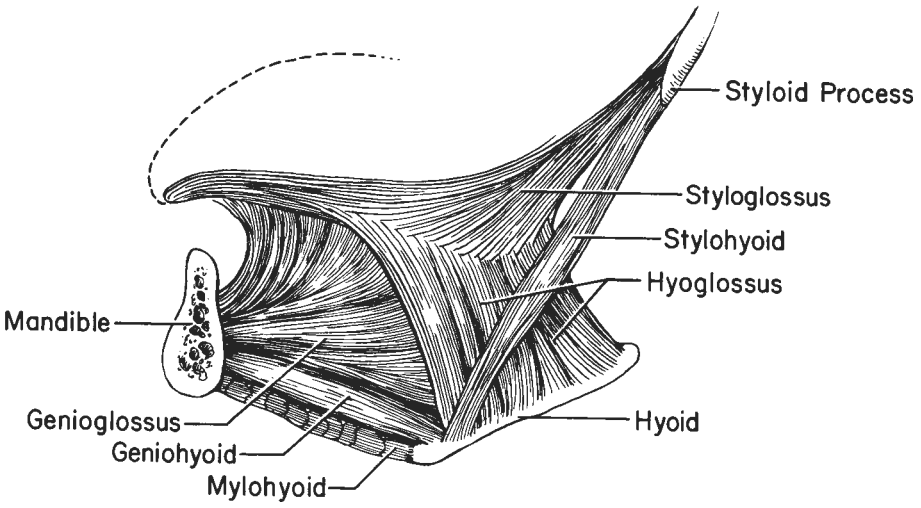


Figure 16-29. Musculature of the tongue and floor of the oral cavity. (Redrawn from Sobotta drawings in Clemente CD. Anatomy: a regional atlas of the human body, ed 3. Baltimore–Munich, Urban & Schwarzenburg, 1987)

squamous epithelium, particularly on the tip and ventrolateral surfaces.

The arterial supply is mainly from paired lingual arteries, which are branches of the external carotid. The midline fibrofatty septum of the tongue is almost complete and restricts anastomosis between the vessels except near the tip of the oral tongue. One lingual artery may be sacrificed without danger of necrosis, but sacrifice of both lingual arteries results in an increased risk for loss of the oral tongue and almost certain loss of the base of the tongue.

The sensory pathway is by way of the lingual nerve to the gasserian ganglion (see Fig. 16-16). The motor nerve is the hypoglossal nerve. The taste buds are supplied by the chorda tympani, a branch of the sensory root of the facial nerve. The lymphatic pathways of the tongue are shown in Figure 16-30.[66] The lingual lymph nodes are shown in Figure 6-8.[56] The lymphatic collecting vessels from the anterior tongue tend to terminate in lymph nodes somewhat lower in the neck than those draining the posterior tongue. A connecting vessel to the submental nodes is rarely seen in adults.[66]

The lymphatic collecting trunks for the outer third of each half of the oral tongue are directed to the ipsilateral submandibular and subdigastric lymph nodes. For the inner two thirds of each half of the tongue, injection of the lymphatics reveals that the central lymphatic collecting vessels come into play, and these vessels have pathways to both sides of the neck (Fig. 16-31). From a practical point of view, as invasion of tumor proceeds more than 5 mm from the lateral margin of the tongue, the risk of contralateral neck metastases gradually increases.

Imaging of the Normal Anatomy

For normal MRI anatomy of the tongue, see Figures 16-11 and 16-12.[39] The oral tongue is loosely attached to the floor of the mouth so it can move freely, and, on axial images, it is somewhat difficult to be sure of the exact zone of transition between the floor of the mouth and ventral surface of the tongue. This is made easier on coronal or sagittal MRI sections or coronal CT sections (see Fig. 16-13). The oral portion of the tongue has a fairly nondescript, homogeneous appearance on CT, mainly of mixed fat and muscle density. On MRI, especially in the sagittal plane, it is usually possible to visualize the various intrinsic muscle bundles and the interleaved fat. The styloglossus muscle interdigitates with the hyoglossus muscle within the posterior aspect of the tongue. The styloglossus muscle can be seen entering the posterior aspect of the tongue and coursing through the fat of the parapharyngeal space from its styloid origin. The muscles and spaces medial and lateral to the styloglossus muscle are potential conduits of tumor spread toward the skull base from the floor of the mouth and tongue base. (See section on normal radiographic anatomy of the floor of the mouth for further discussion.)

Pathology

More than 95% of the oral tongue cancers are squamous cell carcinomas. Coexisting leukoplakia is common. Verrucous carcinoma and minor salivary gland tumors are uncommon. Granular cell myoblastoma is a benign tumor of uncertain origin that commonly occurs on the dorsum of the tongue and may be confused histologically with carcinoma because of the associated pseudoepitheliomatous hyperplasia.

Patterns of Spread

Primary

Nearly all squamous cell carcinomas of the oral tongue occur on the lateral and undersurfaces of the tongue. Rarely, lesions appear on the dorsum, usually in the posterior midline. Most of the lateral border lesions occur on the middle and posterior thirds, with a few on the anterior third. Oral tongue carcinomas tend to remain in the tongue until large. Perineural invasion is seen is about 5% of glossectomy specimens.

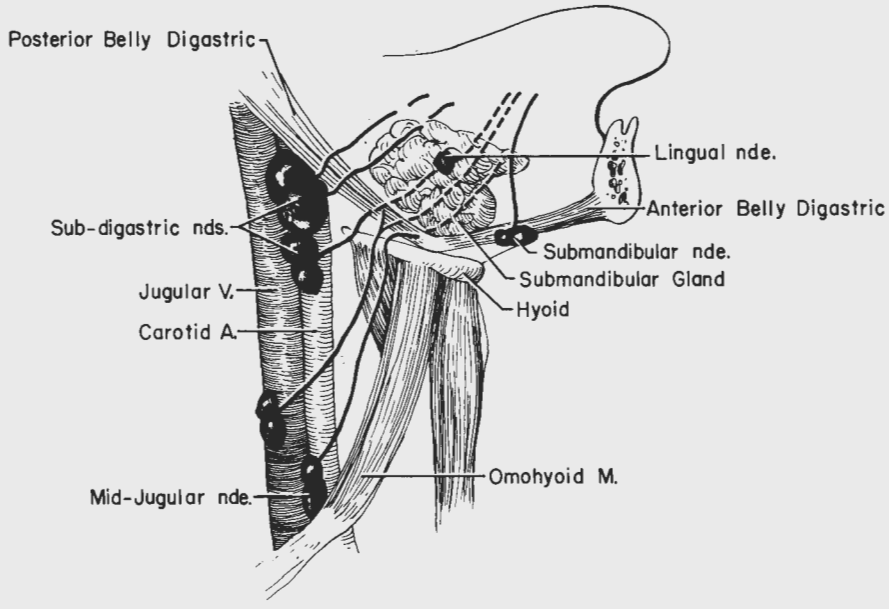


Figure 16-30. Lymphatics of the tongue. (Modified from Rouvière H. Anatomy of the human lymphatic system. Ann Arbor, Edwards Brothers, 1938:45)

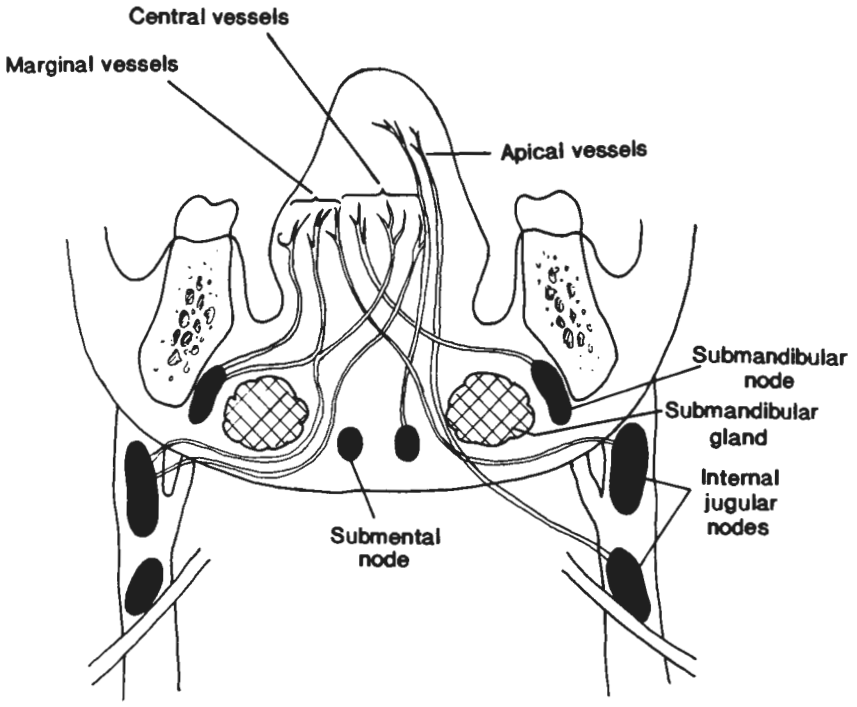


Figure 16-31. Lymphatics of the oral tongue. (Modified from Rouvière H. Anatomy of the human lymphatic system. Ann Arbor, Edwards Brothers, 1938:47)

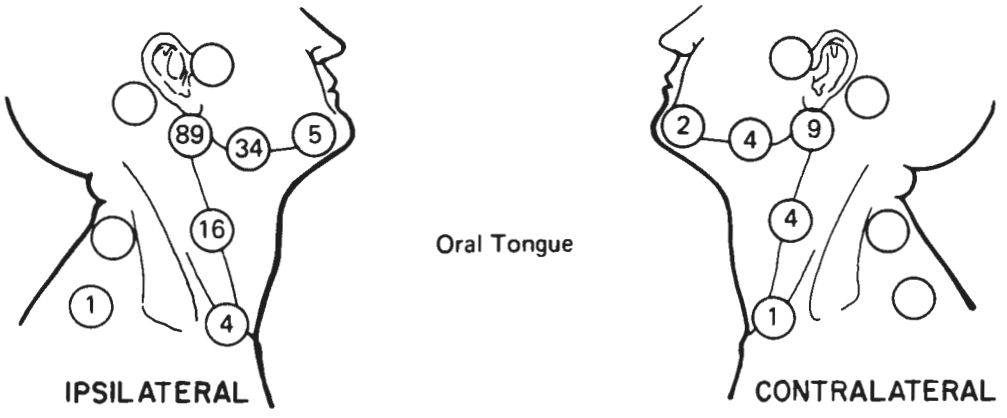
Anterior-third (tip) lesions are usually diagnosed early. Advanced lesions invade the floor of mouth and root of tongue, producing ulceration and fixation. Middle-third lesions invade the musculature of the tongue and later invade the lateral floor of the mouth.

Posterior-third lesions grow into the musculature of the tongue, the floor of the mouth, the anterior tonsillar pillar, the base of the tongue, the glossotonsillar sulcus, and the mandible. Posterior-third lesions behave more like cancer of the base of the tongue with a higher incidence of lymph node metastasis.

Lymphatics

Several studies have correlated the risk of disease in lymph nodes with depth of invasion of the primary lesion (see Chap. 6).

The distribution of nodal metastases on admission is shown in Figure 16-32. Thirty-five percent of patients with cancer of the oral tongue have clinically positive nodes on admission, and 5% have bilateral nodes. The incidence of positive nodes increases with T stage (see Table 6-3).[34] The overall incidence of subclinical disease



N_0	N_1	N_{2A}	N_{2B}	N_{3A}	N_{3B}	N_1-N_3 / Total
197	40	9	32	8	16	105 / 302=35%

Figure 16-32. Carcinoma of the oral tongue: nodal distribution on admission, MD Anderson Hospital, 1948 to 1965. (Lindberg RD. Distribution of cervical lymph node metastases from squamous cell carcinoma of the upper respiratory and digestive tracts. Cancer 1972;29:1448)

is approximately 30% (see Table 6-2). Byers[13] reported a 19% incidence for T1 and T2 lesions and 32% for T3 and T4 lesions after elective neck dissection. The distribution of involved lymph nodes after modified neck dissection for 48 patients with a clinically negative neck is shown in Figure 16-33. The first-echelon nodes are the subdigastric and submandibular. The spinal accessory lymph nodes are seldom involved in the clinically negative neck. Note the 18% risk for midjugular involvement. Rouvière[66] describes lymphatic trunks that bypass the subdigastric and submandibular nodes and terminate in the midjugular (or the lower jugular) lymph nodes (see Fig. 16-31). Submental node involvement is not common and is usually seen with lesions on the tip of the tongue. Patients with N1 or N2 ipsilateral nodes have a 27% risk of developing nodal metastasis in the opposite neck.[24]

Clinical Picture

Presenting Symptoms

Mild to moderate irritation and the sensation of a lump in the tongue are the most frequent complaints. The patient may present to the physician because he thinks he has bitten his tongue. The pain may occur only during eating or drinking. As ulceration develops, the pain becomes progressively worse and may be referred to the external ear canal (see Fig. 16-16). Extensive infiltration of the muscles of the tongue affects speech and swallowing. Patients with advanced lesions have a foul odor. Hemorrhage is uncommon.

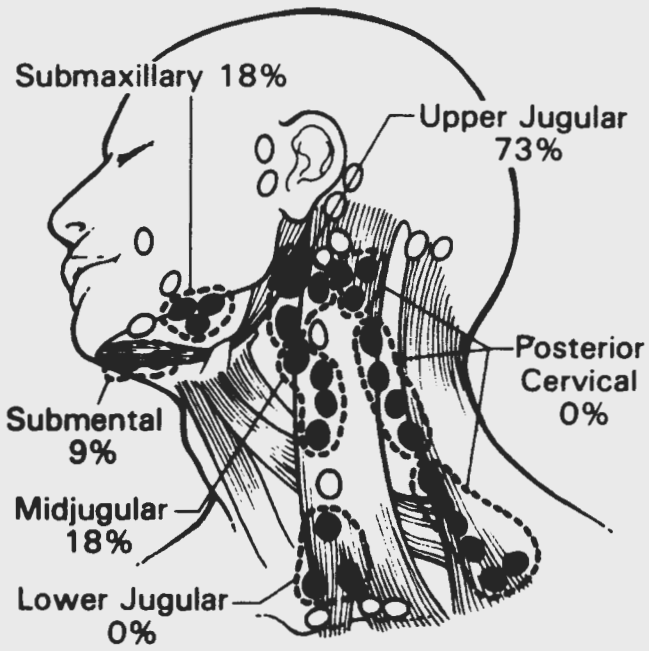


Figure 16-33. The distribution of involved neck nodes after elective modified neck dissection for 48 patients with carcinoma of the oral tongue and a clinically negative neck. (Byers RM, Wolf PF, Ballantyne AJ. Rationale for elective modified neck dissection. Head Neck Surg 1988;10:162)

Physical Examination

The extent of disease is determined by visual examination and palpation. The tongue protrudes incompletely and toward the side of the lesion as fixation develops. Posterior lesions of the oral tongue may grow inferiorly, behind the mylohyoid, and present as a mass in the neck at the angle of the mandible; the mass may be confused with an enlarged lymph node. Atrophy caused by invasion of the hypoglossal nerve is rare. Posterolateral lesions may be difficult to evaluate because of pain; topical anesthesia or general anesthesia may be required for examination. An enlarged submandibular gland may be due to cancer involving the gland or to inflammation due to obstruction of the submandibular duct.

Methods of Diagnosis and Staging

The differential diagnosis includes granular cell myoblastomas, which are usually 0.5- to 2.0-cm, slow-growing, nontender masses. The lesions are well-circumscribed, firm, and slightly raised, and they may be multiple. Malignant behavior is either nonexistent or rare, and wide local excision is the treatment of choice. Pyogenic granulomas mimic small exophytic carcinomas. The papillae foliatae may be hypertrophied secondary to chronic inflammation and may be confused with a carcinoma. Tuberculous ulcer and syphilitic chancre are rare considerations.

Biopsy Technique

A punch forceps biopsy or incisional biopsy is performed with the use of a local anesthetic. Small superficial lesions, less than 1 cm in size, should be completely excised, and margins should be carefully examined by frozen section.

Diagnostic Imaging

The full extent of invasion can sometimes best be determined with CT or MRI. It has been known for many years that the gross margins of a tongue cancer, as seen at surgery, can be deceiving, and tumor may be found far beyond the apparent palpable margins. Although CT and MRI cannot detect microscopic spread beyond the palpable margins of the tumor, it can help to map the gross pattern of spread before surgical or radiation therapy.

Aggressive tumors can, on rare occasions, grow out of the tongue along the styloglossus muscle and extend as far as the styloid attachment of this muscle (Fig. 16-34). Inferior spread to the sublingual space can carry the tumor to the mylohyoid and geniohyoid muscles, with all the implications of spread in the floor of the mouth (see section on the floor of the mouth). Occasionally, cores of tumor growth can radiate from the center of the tumor and spread to the tongue base without any clinical evidence of such involvement.

See the section on diagnostic imaging for the floor of the mouth for recommendations for detection of mandible invasion. Interpretative pitfalls relative to coexistent edema and obstructive sialadenitis in the sublingual and submandibular glands also were discussed in the section on the floor of the mouth.

The entire neck is studied in any patient with tongue cancer (see Chap. 6). See Figure 6-32 for an example of imaging of the lingual lymph nodes.

Figure 16-34. A patient with carcinoma of the posterior oral tongue. (*A*) The tumor (T) infiltrated the tongue substance to a depth of approximately 1.5 cm. Its medial margin (*arrowhead*) did not cross the midline. Note also the obliteration of the tissue planes around the styloid musculature and poststyloid parapharyngeal space (*open arrow*); this area should be carefully compared to the opposite, normal side. (*B*) A section made approximately 2 cm inferior to that in *A* shows tumor streaming out of the tongue along the thickened stylohyoid-hyoglossus complex of muscles (*arrowheads*) to obliterate the tissue planes around the styloid musculature, posterior belly of the digastric, and poststyloid parapharyngeal space (*open arrow*). (*C*) A section made approximately 2 cm below *B* showing continued spread of tumor along the carotid sheath. Clinically, this tumor appeared to be limited to the oral tongue. There was no palpable abnormality in the neck. At operation, the tumor was found extending out of the tongue and encasing the styloid musculature with extension along the carotid sheath to the skull base, where surgical margins contained tumor. Spread, inferiorly along the carotid sheath, was also confirmed surgically.

Staging

For apparent early lesions, physical examination is sufficient for staging. As the lesions enlarge and become painful, examination under anesthesia is often necessary. Imaging evaluation is useful in the larger lesions. The AJCC staging for oral cavity carcinoma was presented at the beginning of this chapter. Mandible invasion or fixation of the oral tongue would place the lesion in the T4 category.

Treatment

Selection of Treatment Modality: Primary Site

Both glossectomy and irradiation are curative for cancer of the oral tongue, and the reported cure rates are similar for similar stages. However, for irradiation to produce satisfactory control rates, the use of interstitial or intraoral cone therapy is essential. If hemiglossectomy is the surgical option, a degree of speech impediment and difficulty in swallowing may be produced, and irradiation may be selected as the initial treatment with partial glossectomy reserved for recurrence. Surgical salvage of irradiation failures is fairly successful for early lesions but drops to a 50% success rate for larger lesions. For this reason, a combination of partial glossectomy and radiation therapy is often advised as initial therapy for the more advanced lesions, although a few patients refuse operation because of the anticipated morbidity.

EXCISIONAL BIOPSY (TX). Excisional biopsy of a small lesion may show inadequate or indeterminant margins. An interstitial implant produces a high rate of control and is favored over reexcision.[4,45] (See section on treatment of lesions of the floor of the mouth after excisional biopsy in this chapter.)

EARLY LESIONS (T1-T2). Operation and irradiation produce similar local control rates, and treatment decisions are based on functional and cosmetic loss, patient preference, and available skills.

Wide local excision is the treatment of choice for well-circumscribed lesions that can be excised transorally. Transoral excision becomes progressively more difficult for lesions of the posterior oral tongue, particularly for those that extend posterior to the insertion of the anterior tonsillar pillar. Irradiation may be selected for larger T1 lesions and for T2 lesions where normal speech is critical (Fig. 16-35). The ideal candidate for irradiation

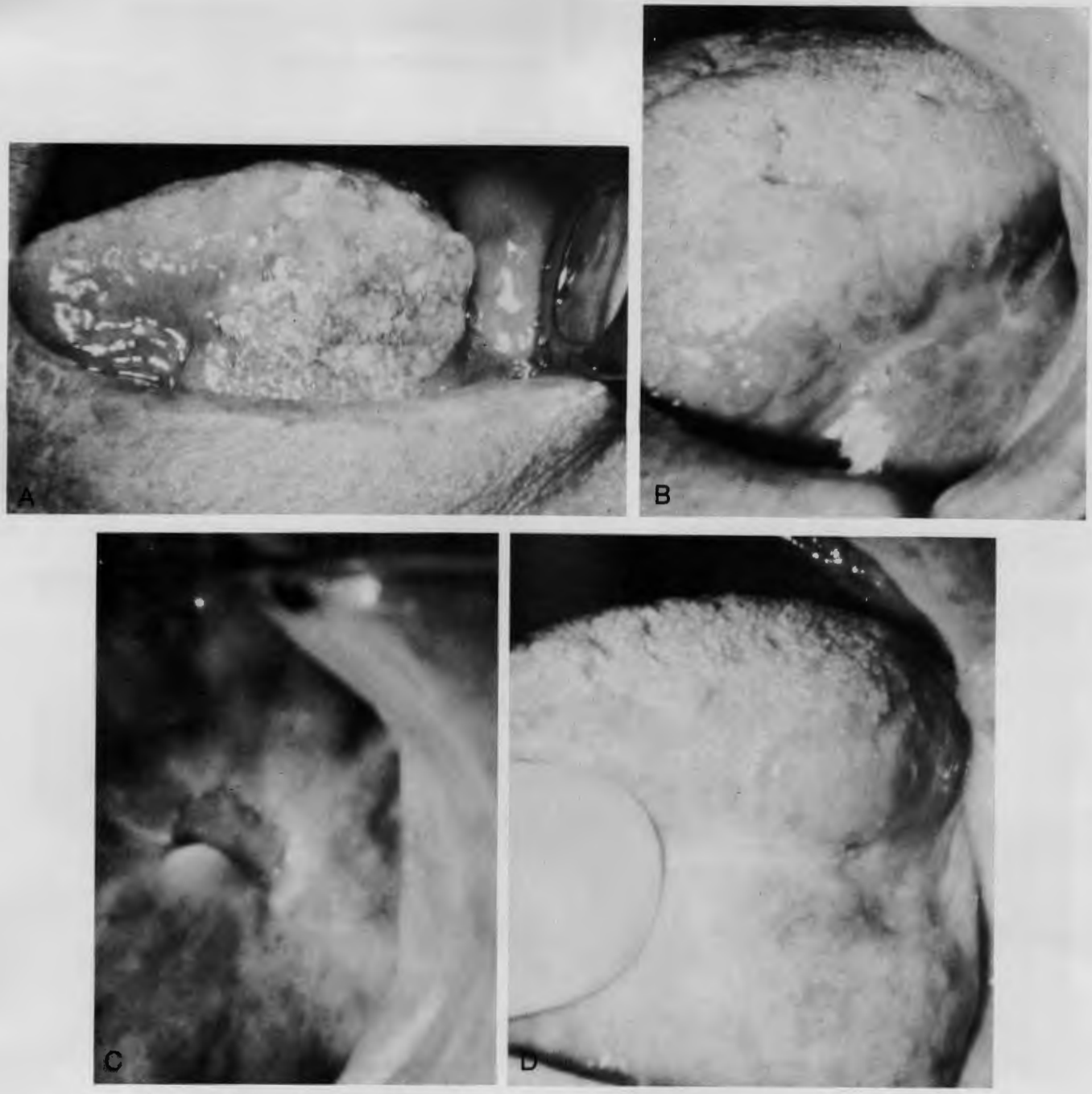


Figure 16-35. (*A*) Squamous cell carcinoma of the oral tongue (T2N0) in a 60-year-old preacher. The patient was treated with a single lateral portal, 3000 cGy over 2 weeks, 2-MV x-rays, followed by a single-plane needle implant for 5000 cGy at 0.5 cm. (*B*) Appearance 1 month after completion of treatment. (*C*) The patient developed a small, painful ulceration on the lateral border of the tongue 1 year after treatment. (*D*) Complete healing 1 month later. There were no further complications. This is an example of a mild (1+) soft-tissue necrosis. The patient continued to preach until his death 10 years later of a cerebrovascular accident.

is edentulous, with the lesion so situated that part of the treatment can be given by intraoral cone; these patients have almost no risk of a bone necrosis. If interstitial therapy is elected, the risk of bone complications is less if the tongue is mobile and can be packed away from the mandible. Posterior oral tongue lesions, in particular, may be selected for radiation therapy.

From the surgical standpoint, it is difficult to determine the extent of tumor invasion into the tongue during the operation; for this reason, preoperative irradiation

Figure 16-36. (*A*) Squamous cell carcinoma of the undersurface of the oral tongue and floor of the mouth with multiple right upper neck nodes, all mobile and small (T3N2B). The lesion was tethered to the mandible, and the tongue could not be fully protruded. The patient received 5000 cGy over 4 weeks, 120 cGy twice a day, to the primary lesion and upper neck nodes and 4050 cGy over 3 weeks to the lower neck nodes. (*B*) At completion of radiation therapy, tumor regression was estimated at 60%. Partial glossectomy, mandibulectomy, and right neck dissection were performed 4 weeks after radiation therapy. Fourteen nodes were positive for disease. The submandibular gland was noted to have tumor that extended into the soft tissue adjacent to the gland. Margins were clear. (*C* and *D*) Anterior and lateral views 6 weeks after operation. The patient was free of disease at 4 years; the only complaint was persistent right shoulder pain. Speech was altered but understandable. Swallowing was not impaired.

(and chemotherapy) should be avoided, because it further obscures the margins and compounds the problem. Whereas a tumor margin of 1 cm is generally considered adequate for most squamous cell carcinomas, the rule of thumb is to take 1.5 to 2.0 cm in the oral tongue.

MODERATELY ADVANCED LESIONS. Lesions that have a large surface involvement, but minimal infiltration, are favorable lesions and can be cured with radiation therapy or partial glossectomy alone. Those lesions that are deeply infiltrative (more than 2 cm in depth) have a slightly higher control rate with combined surgery and radiation therapy, but the patient must be willing to accept partial glossectomy and possibly mandibulectomy (Fig. 16-36).

ADVANCED LESIONS (T4). Combined treatment with surgery and radiation therapy will cure a few patients, especially those with minimal neck disease. Operation usually requires total glossectomy and partial or total laryngectomy. Most patients in this category receive palliative irradiation.

Management of the Neck

The neck is managed according to the guidelines in Chapter 6. When irradiation is selected for the primary lesion, elective neck irradiation is given for patients with a clinically negative neck except in the case of a small, superficial lesion. When an operation is selected for the primary lesion, elective neck dissection is almost always recommended for the clinically negative neck. Small, superficial lesions, less than 1.5 to 2.0 mm thick on microscopic examination, have a small risk of subclinical neck disease and may be observed every 4 to 8 weeks for 2 to 3 years.

Lesions of the tip of the tongue, those that have spread near the midline, and those with ipsilateral involved lymph nodes are at risk for bilateral neck disease.

Surgical Treatment

Partial glossectomy is frequently the initial and only treatment for oral tongue carcinoma. Postoperative irradiation is recommended for positive or close margins, perineural invasion, and large lesions in general. Postoperative irradiation is recommended if the initial surgical margin is positive even if subsequent margins are negative.[67] The surgical approach to early and moderately advanced lesions of the oral tongue is usually transoral. It is more difficult to use the transoral approach for lesions that extend posteriorly. As the lesion is being resected, however, some of the tongue can be pulled further forward so that an adequate posterior margin can be obtained.

For oral tongue lesions extending into the floor of the mouth or into the base of the tongue, the technique of floor release may be used (see section on the base of the tongue in Chap. 17).

EARLY LESIONS (T1-T2). Examples of two lesions and the amount of tongue to be removed are shown in Figure 16-37. The rule of thumb is to take a margin of 1.5 to 2.0 cm around the palpable disease. Speech impediment or difficulty in swallowing would be unlikely in either case. Primary closure is almost always possible (Fig. 16-38). If primary closure is not possible, a split-thickness skin graft usually suffices. Flaps are avoided because they add too much bulk and limit mobility and sensation.

MODERATELY ADVANCED LESIONS (T2-T3). Moderately advanced lesions are managed by glossectomy followed by postoperative radiation therapy in selected cases. The amount of tongue removed and the approach to the oral cavity varies with each case. A margin of 2 cm is difficult to obtain in all situations. It is difficult when cutting the tongue to judge projections of tumor, and the likelihood of cutting across cancer is greater than for the other head and neck sites.

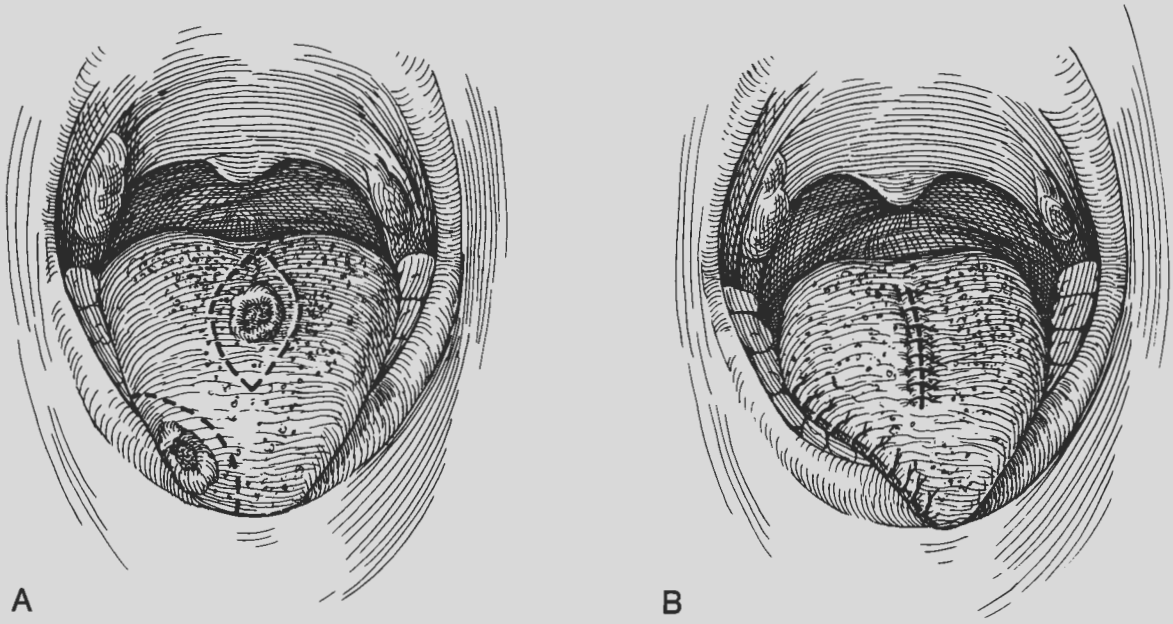


Figure 16-37. Small lesions on the anterior free margin of the tongue or in the midline of the tongue can be excised (*A*) and the defect closed primarily (*B*). (Million RR, Cassisi NJ, Clark JR. Cancer of the head and neck. In: DeVita VT Jr, Hellman S, Rosenberg SA, eds. Cancer: principles and practice of oncology, ed 3. Philadelphia, JB Lippincott, 1989:515)

Figure 16-38. (*A*) Squamous cell carcinoma of the right lateral oral tongue (T1N0). (*B*) Wide local excision. (*C*) Primary closure.

It is an advantage to the surgeon to be able to feel the tumor mass to obtain a wide margin; this is not possible if radiation therapy or chemotherapy has produced significant regression before glossectomy. Finally, if the mandible must be sacrificed after preoperative radiation therapy, the likelihood of fistula, exposed bone, and osteomyelitis is increased.

ADVANCED LESIONS (T4). Advanced lesions require either a total glossectomy and partial or total laryngectomy or total glossectomy with myocutaneous flap reconstruction; postoperative radiation therapy would usually be recommended. Total glossectomy is only offered to patients in good general condition and with minimal neck disease.

Irradiation Technique

The dose guidelines are given in Table 16-19.

Control of the primary lesion is enhanced by giving all or part of the treatment by interstitial radiation therapy[16,27,31,33,47] or intraoral cone and when the overall treatment time is less than 40 days. Treatment of the neck is an integral part of the treatment plan and is outlined in Chapter 6. Elective neck irradiation is recommended for nearly all tongue lesions; 3000 cGy in 10 fractions over 2 weeks to the tongue and neck is recommended to keep the overall time under 40 days; this dose has been sufficient for subclinical neck disease.

INTRAORAL CONE IRRADIATION. Intraoral cone therapy in appropriate cases produces similar local control rates compared to interstitial treatment and has the added advantage of less dose to the mandible and no hospitalization for an implant. It may be used in the cooperative patient with a lesion with discrete borders, mainly exophytic and 2 cm or less in thickness. The patient holds the tongue during the therapy. Edentulous patients are usually easy to treat, but those with teeth may be difficult or impossible. The cone therapy is done before the external beam to avoid a sore mouth and to see the lesion clearly through the periscope. Local anesthesia is usually not needed.

Either orthovoltage or electrons may be used; our preference is orthovoltage. If electrons are used, bolus is needed. The daily dose with orthovoltage (250 kV, 0.5-Cu

TABLE 16-19. Irradiation Guidelines for Carcinoma of the Oral Tongue at the University of Florida

Clinical Stage	Interstitial Alone	External Beam Plus Interstitial
TX—No visible or palpable tumor	6000	Not recommended
TX—Palpable induration or nodularity	7000	3000 over 2 wk plus 3500
Early (<1 cm)	6500	3000 over 2 wk plus 3500
Early (1–3 cm)	Not recommended	3000 over 2 wk plus 3500
Moderately advanced (3–5 cm)	Not recommended	3000 over 2 wk plus 4000
Advanced	Not recommended	5000 plus 3500
Postoperative radiation therapy	See Chapter 5	
Preoperative radiation therapy	See Chapter 5	

(Modified from Million RR, Cassisi NJ, Clark JR. Cancer of the head and neck. In: DeVita VT Jr, Hellman S, Rosenberg SA, eds. Cancer: principles and practice of oncology, ed 3. Philadelphia, JB Lippincott, 1989:515)

filter) is 300 cGy, for a dose of 2100 to 2700 cGy in 7 to 9 days; megavoltage external-beam treatment follows with 3000 cGy in 10 fractions over 2 weeks. Small, superficial lesions may be managed by intraoral cone therapy alone, 4800 cGy in 16 fractions over 3 weeks.

INTERSTITIAL IRRADIATION. Interstitial irradiation may be used to deliver the entire dose, or it may be used in conjunction with external irradiation. Historically, the external-beam therapy has preceded the implant. The implant is done within 1 week of completion of the external-beam therapy. Implants are usually arranged in planes or modified planes. A single-plane implant is seldom adequate even for superficial lesions. A two-plane implant is used for lesions up to 1.0 to 1.5 cm thick, and a volume or three-plane implant is used for larger lesions. The implant covers the gross extent of the lesion plus a margin of normal tongue.

The iridium hairpin technique devised by Pierquin[62,63] is our current preferred technique. The patient is sedated and placed in the sitting position in the operating suite. A dentist performs block anesthesia. Gutter guides (1.2-cm spacing) are placed approximately 1.0 to 1.5 cm apart starting at the posterior portion of the implant area. A C-arm fluoroscope is used to monitor the position of the guides (Fig. 16-39). Hairpins of ^{192}Ir are

Figure 16-39. Lateral (*left*) and anteroposterior (*right*) views of ^{192}Ir implant for carcinoma of the left side of the oral tongue, stage T2N0, measuring 3.5 × 2.0 × 2.0 cm, with submucosal extension to within 0.5 cm of the midline of the tongue. Treatment consisted of 3000 cGy in 10 fractions followed in 1 week by the implant. The gutter-guide technique was used with the patient in a sitting position, with a combination of local anesthesia and regional nerve block. Fluoroscopy was used in the operating room to verify accurte source spacing and alignment. The implant sources were 4 cm long. A gauze pack was secured into the lateral floor of the mouth to displace the tongue medially away from the mandible. The implant remained in place for 73 hours and delivered 4000-cGy tumor dose to the area of gross disease (55 cGy per hour). The patient remained free of disease at 20 months. (Parsons JT, Mendenhall WM, Bova FJ, Million RR. Head and neck cancer. In: Levitt SH, Khan FM, Potish RA, eds. Levitt and Tapley's technological basis of radiation therapy: practical clinical applications, ed 2. Philadelphia, Lea & Febiger, 1992:221)

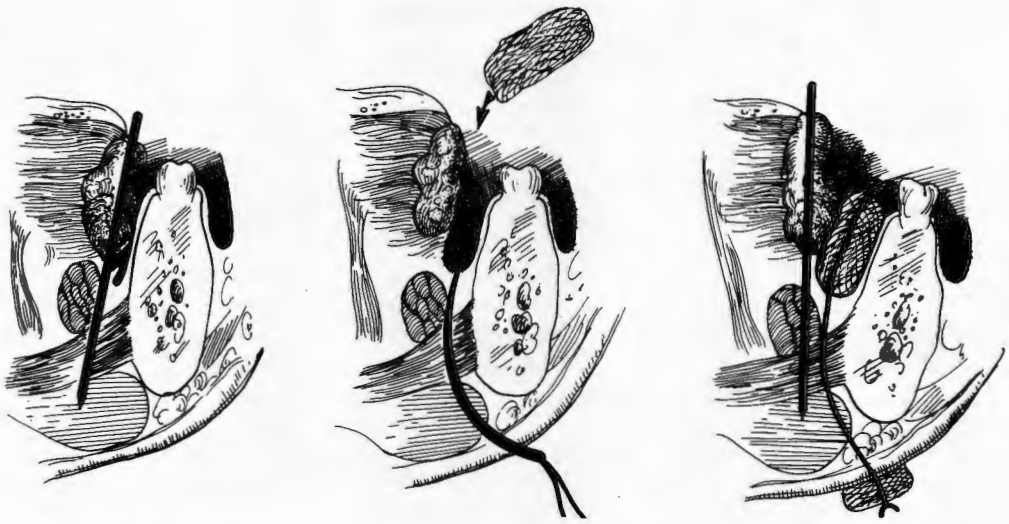


Figure 16-40. Use of packing to reduce dose to mandible. (*Left*) Implant without packing. (*Center*) Large curved needle inserted through skin to floor of the mouth. (*Right*) Gauze pack tied to suture and secured between mandible and tongue after implant is completed.

inserted in the gutter guides, a silk suture placed around each hairpin, and the gutter guides are removed. This technique is preferred to rigid needles because there is less discomfort for the patient; it can be done under local or general anesthesia with the patient seated (for better exposure); the radiation exposure is similar or less compared to techniques with needles mounted in bars; and it is technically easier to perform.[58]

Figure 16-41. Radium needles mounted in a rigid device for implantation of oral tongue cancer. The holders were originally fashioned from stainless steel or aluminum, but more recently nylon has proved more satisfactory. The needles are secured to the bar with half-hard stainless steel wire passed through the eyelets. An Allen forceps has been drilled to grasp the needles. Crossing needles may be attached to the bar or inserted separately. Cesium needles have replaced the radium sources. (Ellingwood KE, Million RR, Mitchell TP. A preloaded radium needle implant device for maintenance of needle spacing. Cancer 1976;37:2859)

The dose to the mandible and gingiva may be significantly reduced by inserting a pack into the floor of the mouth, as shown in Fig. 16-40.

If radium or cesium needles are used, they may be mounted in a holder to maintain proper spacing and improve alignment (Figs. 16-41 and 16-42).[20] The mounted needles are relatively easy to implant for a single lateral plane, but it requires some dexterity and maneuvering to insert the medial plane, particularly if the oral cavity is small, if the tongue is large, and if teeth are present. (This technique has mostly been abandoned for oral tongue tumors but is still used for small boost implants.)

Tracheostomy is not necessary on a routine basis, but is advised for appropriate cases. The tongue may enlarge during or immediately after the implant; methylprednisolone sodium succinate (Solu-Medrol) may be given intravenously in the recovery room with rapid reduction of tongue size.

Radioactive sources are sutured in place with 2-0 silk. The sutures exit the mouth and are sutured to the skin of the cheek; this aids in finding the knots when the time comes to remove the implant.

Control of oral tongue lesions is significantly improved if a greater proportion of the treatment is by interstitial therapy (Fig. 16-43). A time–dose analysis for T2 lesions is presented in Figure 16-44; completion of treatment in less than 40 days is shown to be critical in predicting success.[46]

The treatment scheme that gives the best results is 3000 cGy in 10 fractions over 2 weeks followed by the implant. This plan gives a sufficient dose for subclinical disease in the lymphatics and completes the entire treatment in 3 to 4 weeks.

EXTERNAL-BEAM IRRADIATION. A single ipsilateral portal or parallel opposed fields are used depending on the size of the primary lesion, the presence or absence of nodes, and the proportion of the dose planned by external-beam therapy; opposed fields are the most common (Fig. 16-45). The tongue is depressed away from the palate, either with a tongue depressor taped to a cork

Figure 16-42. A 51-year-old man presented with a 3-month history of a painful sore on the right dorsum of the tongue. The lesion measured 3 ×2 cm and extended near the midline. Biopsy revealed squamous cell carcinoma (T2N0). The patient refused glossectomy. Treatment plan: (1) Opposed lateral portals, 3000 cGy over 2 weeks, ^{60}Co. (2) Radium needle implant for 4500 cGy. (*A*) Squamous cell carcinoma on dorsum of oral tongue. (*B*) Insertion of lateral row of radium needles. The needles were mounted in a nylon bar. There were two crossing needles in the lateral bar and one crossing needle in the medial bar. The nylon holder assisted in maintaining the active portion of the needles above the lesion to give an adequate dose to the dorsum of the tongue. (*C*) Radium implant in place. (*D*) Mucositis at 2 weeks. (*E*) Complete healing at 3 months. There was no evidence of disease at 8 years.

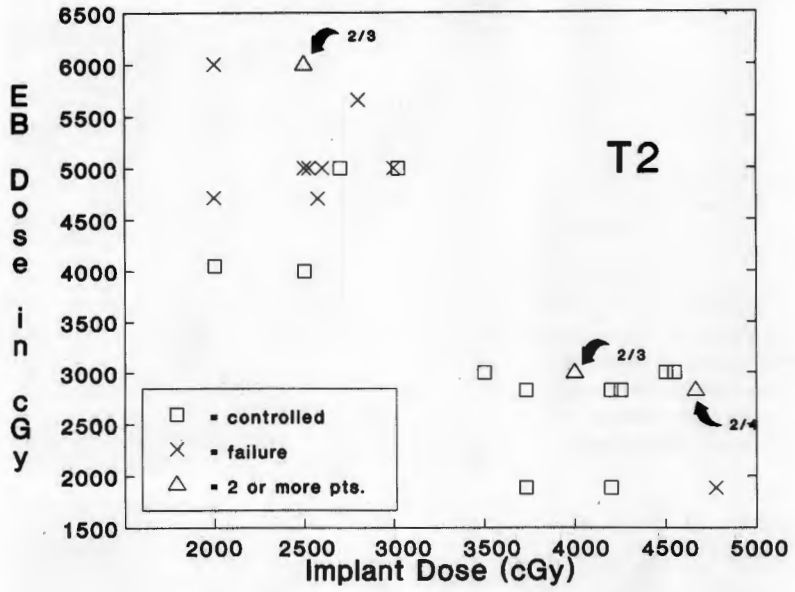


Figure 16-43. Local control of T2 oral tongue carcinoma as a function of external-beam dose versus interstitial implant dose for patients treated with both external beam and implant. EB, external beam. (Mendenhall WM, Parsons JT, Stringer SP, Cassisi NJ, Million RR. T2 oral tongue carcinoma treated with radiotherapy: analysis of local control and complications. Radiother Oncol 1989;16:278)

or by a lead shield. The portal includes the submandibular and subdigastric lymph nodes if the neck is clinically negative; the submental lymph nodes are included for lesions near the tip of the tongue. The posterior border is at least 2 cm behind the sternocleidomastoid muscle. The portal is enlarged for clinically palpable lymph nodes. The lower neck is treated through an anterior portal with a larynx shield (Fig. 16-46).[58,60] A metal pin is inserted into the anterior and posterior borders of the lesion under local anesthesia to assist in external-beam treatment planning and in the placement of interstitial sources (see Chap. 14). Mucosal tattoos may be tried, but occasionally there is diffuse spread of the tattoo ink resulting in a permanent patch of blue mucosa. We have stopped using tattoos. If the patient has teeth with metal fillings that lie against the tongue or buccal mucosa, a thin layer of cotton or gauze is inserted between the teeth and tongue or buccal mucosa to prevent a high-dose effect. The anterior skin and subcutaneous tissues of the submental area should be shielded when possible to reduce submental edema and late fibrosis. The dose of 3000 cGy in 10 fractions over 2 weeks is preferred in conjunction with implant or intraoral cone because of a higher success rate for the short overall time as compared with other plans.[47] A small (1- to 2-cm) clinically positive lymph node would require a boost. Larger lymph nodes are usually managed by a planned neck dissection (see Chap. 6).

Combined Treatment Policies

When glossectomy is selected, the operation is usually performed first. Even without previous irradiation, the surgeon has a difficult time estimating tumor extent in the tongue. The major indication for preoperative irradiation is a large fixed node, in which case it is hoped that the irradiation will encapsulate the mass and allow surgical clearance. An interstitial implant may be used to

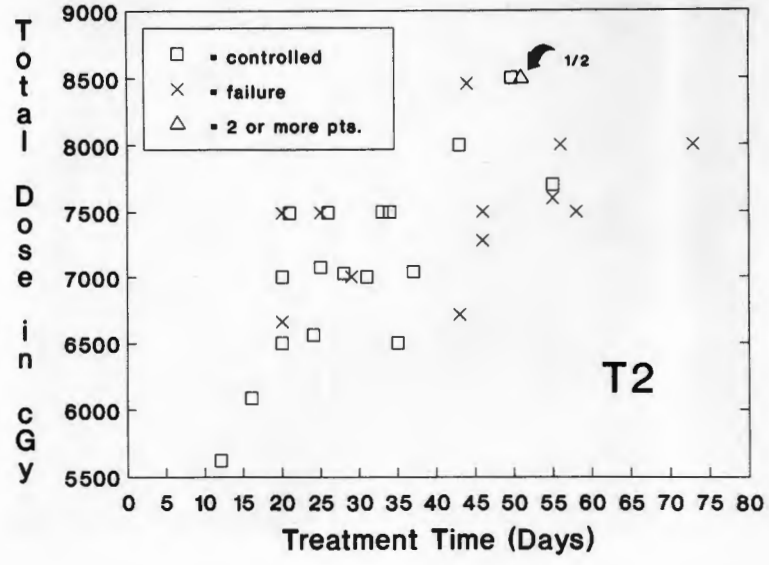


Figure 16-44. Local control of T2 oral tongue carcinoma as a function of total dose versus overall treatment time for patients treated with external beam and implant. (Mendenhall WM, Parsons JT, Stringer SP, Cassisi NJ, Million RR. T2 oral tongue carcinoma treated with radiotherapy: analysis of local control and complications. Radiother Oncol 1989;16:278)

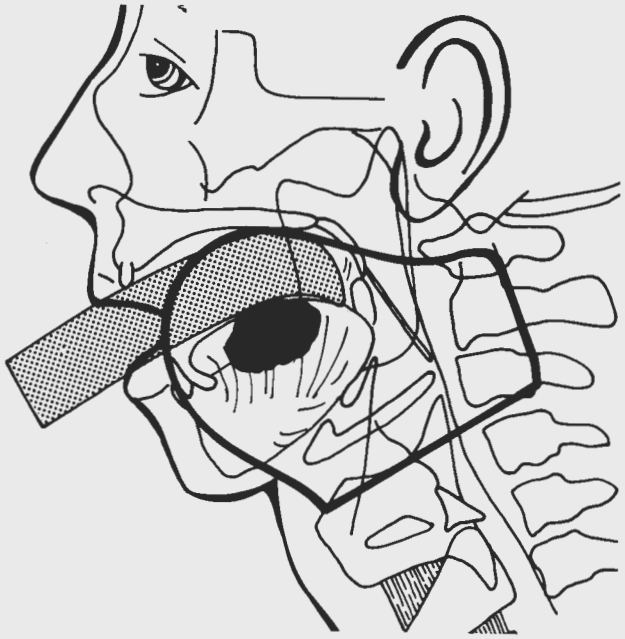


Figure 16-45. Example of portal for carcinoma of the oral tongue with an N0 neck. The field encompasses the submental, submandibular, and subdigastric lymph nodes; the sternocleidomastoid muscle plus 1 cm is included to ensure adequate posterior coverage of the subdigastric lymph nodes. Stainless-steel pins are usually inserted into the anterior- and posterior-most aspects of the lesion to aid in localizing the cancer on the treatment planning (simulation) roentgenogram and to confirm coverage by the interstitial implant. The larynx is excluded from the radiation field. The anterior submental skin and subcutaneous tissues are shielded when possible to reduce submental edema and late fibrosis. The upper border is shaped to exclude part of the parotid gland. An intraoral lead block (stippled area) may be used in selected cases to shield the contralateral mucosa. The block is coated with beeswax to prevent a high-dose effect on the adjacent mucosa due to scattered low-energy electrons from the metal surface. The usual preinterstitial tumor dose is 3000 cGy in 10 fractions. An ipsilateral portal may be selected for superficial lesions; larger lesions are managed with parallel opposed portals without an intraoral lead block. The lower neck is electively irradiated in all cases. (Parsons JT, Million RR. Radiation therapy of tumors of the oral cavity. In: Thawley SE, Panje WR, eds. Comprehensive management of head and neck tumors. Philadelphia, WB Saunders, 1987:529)

deliver a portion of the dose to the tongue if radiation therapy is given before an operation. Postoperative irradiation should usually begin within 6 to 12 weeks. Parallel opposed portals to include the tongue and upper neck to the level of the thyroid notch is the most common plan. The lower neck is irradiated through an anterior portal with a larynx shield. Because most of the oral cavity is irradiated, the dose per fraction is 180 cGy per day, with a total dose of 6000 to 6500 cGy for negative margins. Interstitial implants are not usually employed in postoperative radiation therapy because recurrences may appear at any point along the surgical dissection. If the margins in the tongue are close or positive, or perineural involvement is present, a dose of 7000 cGy (using one fraction per day) is preferred because of the difficulty of eradicating even small amounts of tumor in the tongue after glossectomy.[2,7,49]

Twice-daily fractionation has been adopted recently to try to improve the control rates in the postoperative oral cavity cases. Split-course therapy should be avoided, because the failure rates are increased.[1]

Management of Recurrence

Most recurrences appear in the first 2 years. Local recurrence after radiation therapy or surgery is heralded by ulceration, pain, increased induration, or obvious exophytic cancer. A trial of antibiotics such as tetracycline often reduces the pain of either radiation necrosis or recurrent tumor. Recurrences have a slightly elevated or rolled border, whereas radiation necroses usually have minimal or no elevation of the border. The induration associated with necrosis is usually less than with recurrence. Contrary to the situation with lesions of the floor of the mouth, biopsy should be done as soon as ulceration appears if the ulcer occurs within the original cancer site, because little or no increased morbidity is likely from the biopsy. Ulcers that appear on adjacent normal tissues (eg, the gingiva) are due to radiation effect and not to cancer. CT and MRI cannot reliably differentiate between radiation necrosis and recurrence in many cases, especially on a single study. Outpatient biopsies performed using a local anesthetic may miss the tumor. If suspicion remains high for local recurrence after a negative biopsy, deep, generous biopsies during a general anesthetic are required, and even this maneuver occasionally misses persistent tumor. Serial imaging studies showing progressively enlarging masses at the primary site or new cervical metastases strongly suggest recurrence.

Irradiation failure is managed by glossectomy (Fig. 16-47). The patient with a surgical failure is occasionally salvaged by radiation therapy or an operation, if the recurrence is limited in extent. Recurrence in soft tissues of the neck is rarely eradicated by any procedure.

Lymph nodes appearing in a previously untreated neck are managed by neck dissection with or without postoperative radiation therapy.

Results of Treatment

Mendenhall and associates[45] reviewed nine patients treated with irradiation after excisional biopsy; seven of eight evaluable patients were cured. Seven of the nine received elective neck irradiation before implant, and there were no neck failures.

Ange and coworkers[4] reviewed 17 patients treated by irradiation after excisional biopsy. All patients had control of the primary lesion. Two patients subsequently developed disease in the neck and were salvaged by surgery.

The local control and 5-year survival rates for 92 patients treated at the University of Florida initially by irradiation are shown in Tables 16-20 and 16-21. The local control rates are improved by treatment times less than 40 days and use of intraoral cone or implant. The local control rate for T2 oral tongue carcinoma managed by at least 3500 cGy by implant plus 2000 to 3000 cGy by external-beam therapy was 75% (12 of 16) (see Fig. 16-43). Approximately 20% of patients die of intercurrent disease, and 10% die of distant metastases.

The local control rates reported by M.D. Anderson Hospital for 268 patients treated initially by glossectomy

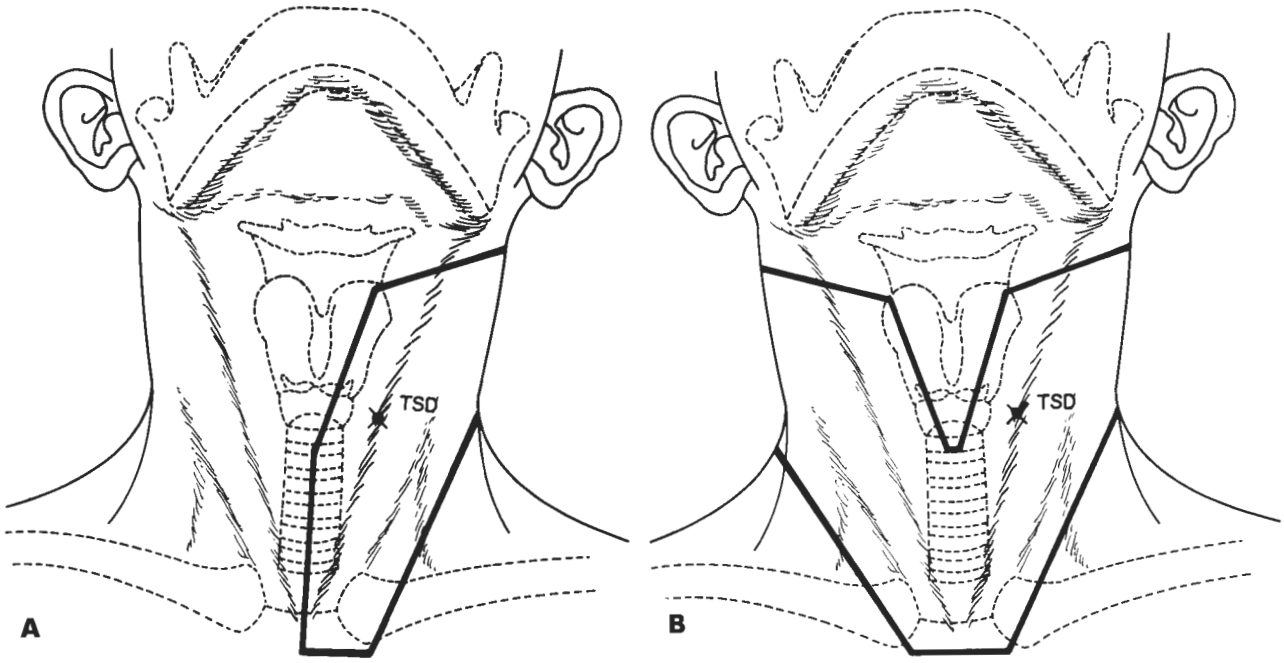


Figure 16-46. (*A*) For well-lateralized lesions and a clinically negative neck, only the ipsilateral low neck is irradiated. (*B*) Portal for elective bilateral lower neck irradiation (see Chap. 6 for design details). (*A* from Parsons JT, Million RR. Radiation therapy of tumors of the oral cavity. In: Thawley SE, Panje WR, eds. Comprehensive management of head and neck tumors. Philadelphia, WB Saunders, 1987:529. *B* from Parsons JT, Million RR. Treatment of tumors of the oropharynx: radiation therapy. In: Thawley SE, Panje WR, eds. Comprehensive management of head and neck tumors. Philadelphia, WB Saunders, 1987:696)

are shown in Table 16-22. There was no difference in local control by T stage when postoperative radiation therapy was added for adverse findings in 14% of cases.[67] Of patients with a T1 or T2 lesion, 17% had initially positive margins and 3% remained positive at the end of the operation. Of those with a T3 or T4 lesion, 28% had initially positive margins and 8% remained positive at the completion of the operation. After surgery only, the local recurrence rate was 13% for those initially negative compared with 22% for those negative after additional resections ($P = .03$). Positive mucosal margins and positive muscular margins had a similar prognosis for local recurrence. The 5-year survival rate in the initially negative group was 49% compared with 31% for those ultimately negative ($P = .02$). Postoperative radiation therapy reduced the overall local recurrence rate to 5%. Patients with perineural invasion were more likely to have a positive margin.

O'Brien and coworkers[55] reported a 5-year disease-free survival of 73% for T1N0 and 62% for T2N0 for 97 patients treated by partial glossectomy alone.

Decroix and Ghossein[19] reviewed 602 previously untreated patients with squamous cell carcinoma of the oral tongue treated by irradiation between 1959 and 1972. Fifty-two percent were treated by radium implant only, 25% by external radiation therapy and implant, 11% by implant followed immediately by local excision of a persistent lesion, 11% by external beam only, and 1% by surgery. Sixty-four percent had a clinically negative neck. Table 16-23 shows the results at 5 years by UICC

TABLE 16-20. Carcinoma of the Oral Tongue—Local Control (Number Controlled/Number Treated)—92 Patients*

Stage	Excluded†	Control With Irradiation	No. Salvaged/ No. Attempts	Ultimate Control
T1	6	8/10 (80%)	1/2	9/10 (90%)
T2	7	21/35 (60%)	5/10	26/35 (74%)
T3	3	10/24 (42%)	3/8	13/24 (54%)
T4	2	0/5	0/1	0/5

* Treated with interstitial implant and/or continuous-course external-beam irradiation.

† Died within 2 years of treatment with primary site continuously disease-free.

Note: University of Florida data; patients treated October 1964 to June 1986; analysis June 1988 by WM Mendenhall, MD.

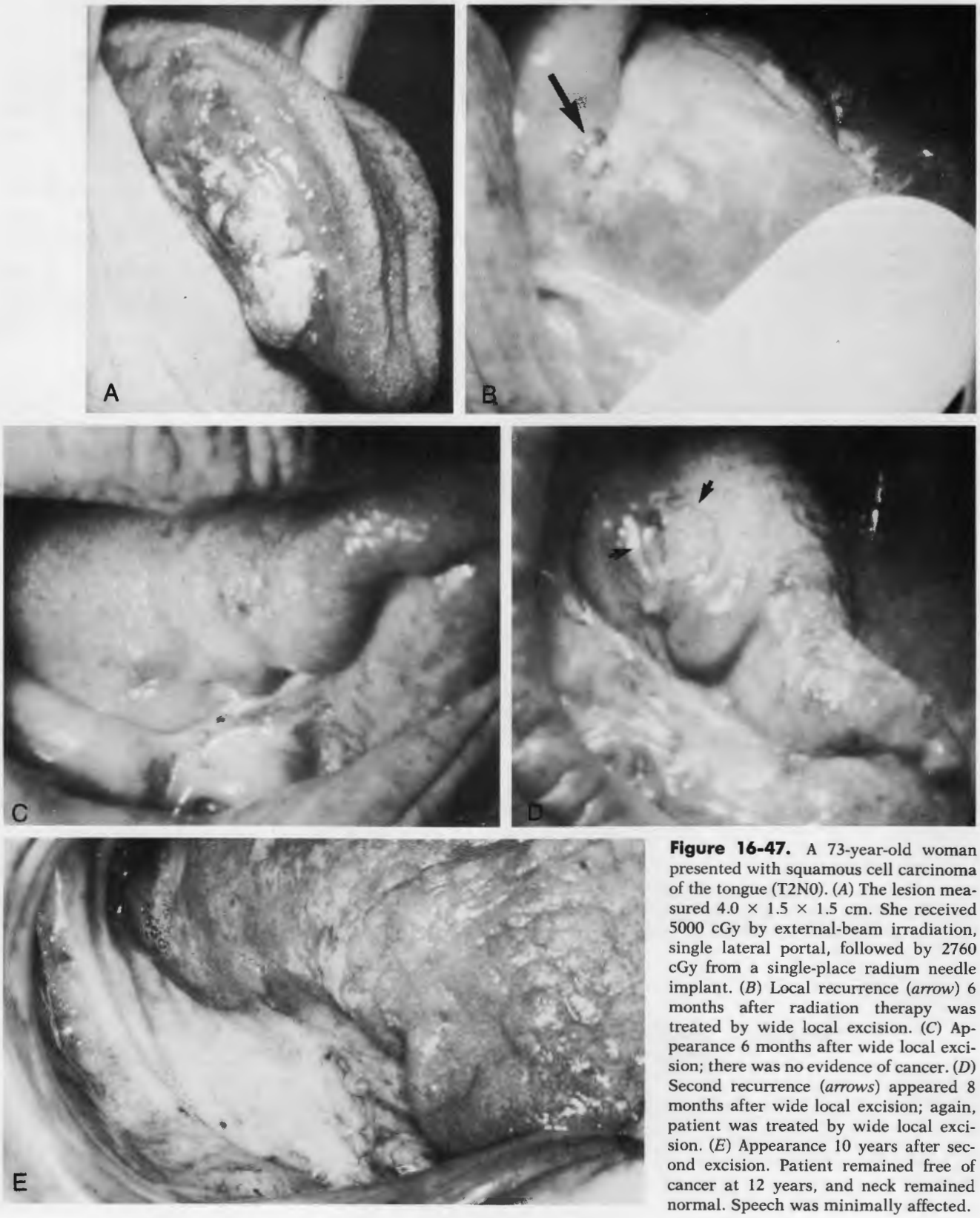


Figure 16-47. A 73-year-old woman presented with squamous cell carcinoma of the tongue (T2N0). (*A*) The lesion measured 4.0 × 1.5 × 1.5 cm. She received 5000 cGy by external-beam irradiation, single lateral portal, followed by 2760 cGy from a single-place radium needle implant. (*B*) Local recurrence (*arrow*) 6 months after radiation therapy was treated by wide local excision. (*C*) Appearance 6 months after wide local excision; there was no evidence of cancer. (*D*) Second recurrence (*arrows*) appeared 8 months after wide local excision; again, patient was treated by wide local excision. (*E*) Appearance 10 years after second excision. Patient remained free of cancer at 12 years, and neck remained normal. Speech was minimally affected.

TABLE 16-21. Carcinoma of the Oral Tongue: 5-Year Survival

AJCC Stage	Absolute	Cause-Specific
I	7/13 (54%)	7/9
II	16/22 (73%)	16/21 (76%)
III	8/24 (33%)	8/19 (42%)
IVA	1/11 (9%)	1/8
IVB	1/8	1/5

Note: University of Florida data; patients treated with interstitial implant and/or continuous-course external-beam irradiation between October 1964 and June 1986; analysis June 1988 by WM Mendenhall, MD.

stage. Sixty-six percent of local recurrences occurred within the treated volume, and 33% occurred at the periphery. A higher percentage of T1 lesions failed at the periphery, suggesting an underestimate of tumor extent for small lesions. There was no difference in local recurrence rates between tumors on the dorsum, the inferior surface, or the lateral border. Only 19 (13%) of 141 patients with local recurrences were alive and free of disease at 5 years. Fifteen of 45 patients were salvaged by operation, and 4 of 24 were salvaged by reirradiation. Complications requiring an operation occurred in four patients; soft tissue necrosis (less than 2 cm) treated conservatively occurred in 24%, and mandible necrosis (less than 2 cm) managed conservatively occurred in 13%. The necrosis rate increased with tumor size.

Wang[79] reported a local control rate of 90% for T1N0 and 85% for T2N0 lesions managed with electron-beam intraoral cone therapy.

Fakih and associates[21] carried out a randomized trial of elective versus therapeutic neck dissection in stages I and II oral tongue cancer. The disease-free survival rate (minimum 1-year observation, median follow-up 20 months) was 52% for the therapeutic arm as compared with 63% for the elective neck dissection arm. More importantly, in the subgroups with primary tumor depth of 4 mm or greater, the disease-free survival was 38% for the therapeutic neck dissection as compared with 55% for elective surgery.

Follow-Up Policy

The recurrence rate at the primary site and in the untreated neck is substantial for all but the smaller lesions; early recognition of recurrence leads to an improved chance of salvage. Follow-up is recommended every 4 to 8 weeks for 2 years, every 3 months for the third year, and then every 6 months.

Surgical failures that occur on the mucosa are easy to detect, but those appearing deep in the operative field initially produce vague induration that is similar to postoperative induration. The appearance of pain should be considered recurrent cancer until proved otherwise.

Radiation failures almost always appear at the site of the original lesion. An ulcer may represent necrosis or recurrence, and biopsy is required to establish the diagnosis.

Complications of Treatment

Surgical Treatment

Orocutaneous fistula, dysphagia, and dysarthria are the three most common sequelae of glossectomy. Damage to the lingual or hypoglossal nerves, although rare, increases the difficulty in swallowing and in speaking. Numbness may occur and interfere with swallowing.

Fistulas and flap necrosis must be handled judiciously because the danger of carotid artery hemorrhage increases with either of these complications.

Enunciation difficulties occur whenever the tongue is bound down by scarring; secondary procedures can frequently improve mobility. The incidence of complications increases for surgical salvage attempts after irradiation failure; the patient must be informed that multiple procedures may be necessary.

Radiation Therapy

Many patients complain of a sensitive tongue for many months after completion of treatment, even when the mucosa is healed. This is hardly surprising because the tongue has been "burned" and, like any other burned area, remains sensitive for a period of time. This effect usually disappears with time.

Taste reappears from 1 week to several months after treatment. Taste may return to normal, but more fre-

(text continues on page 378)

TABLE 16-22. Carcinoma of the Oral Tongue: Local Failures According to Initial Frozen-Section Margin*

	TX	T1	T2	T3	T4	Total
Surgery only						
Initially negative	2/10	9/72	4/48	5/23	0/4	20/157 (13%)
Ultimately negative	0/1	3/9	2/8	0/7	1/2	6/27 (22%)
Postoperative radiotherapy						
Initially negative	0/0	0/2	0/10	2/11	0/6	2/29 (6%)
Ultimately negative	0/0	0/1	0/3	0/2	0/2	0/8 (0%)

* Slashed values indicate the number of patients in each tumor stage with the margin specified/total number of patients in each tumor stage.

(Scholl P, Byers RM, Batsakis JG, Wolf P, Santini H. Microscopic cut-through of cancer in the surgical treatment of squamous carcinoma of the tongue. Am J Surg 1986;152:356)

TABLE 16-23. Carcinoma of the Oral Tongue Treated by Irradiation—602 Patients

UICC Stage	Patients	Local Recurrences	Neck Failure Alone	Patients Salvaged, No Evidence of Disease at 5 Years	5-Year Survival	
					Absolute	Cause-Specific
T1 (≤2 cm)	94	14%	11%	6	57%	80%
T2 (>2–4 cm)	288	22%	10%	10	41%	56%
T3 (>4 cm)	220	29%	11%	3	18%	25%

(Modified from Decroix Y, Ghossein NA. Experience of Curie Institute in treatment of cancer of the mobile tongue. 1. Treatment policies and results. Cancer 1981;47:500)

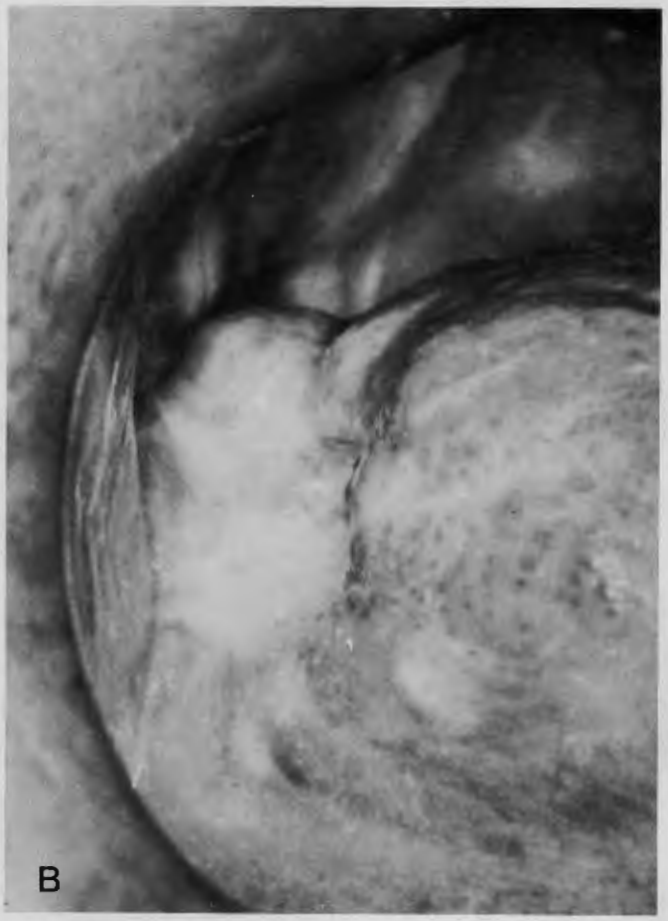


Figure 16-48. (*A*) Ulcerated squamous cell carcinoma of the posterior lateral oral tongue (T3N2B). Patient refused operation. Treatment was 7000 cGy over 7 weeks, ^{60}Co, plus a radium implant for 2000 cGy. (*B*) Appearance 3 months after radiation therapy. Soft tissue necrosis was present with pain. There was induration beneath the necrosis. Patient steadfastly refused surgery in case of proven recurrence, so biopsy was not done. (*C*) Appearance 16 months after radiation therapy. Pain persisted intermittently, but healing gradually progressed so that he was free of pain by 1½ years and the ulcer was healed. The patient died of lung cancer 2½ years after treatment of his tongue; there was no recurrence of his tongue cancer.

Figure 16-49. (*A*) A 60-year-old man had a carcinoma of the left lateral border of the tongue measuring 3 × 2 cm (T2N0). He was treated with 3000-cGy tumor dose over 2 weeks followed by a two-plane radium needle implant delivering 5000 cGy. (*B*) There was initial healing of the lesion, but, at 4 months, the patient returned with a deep ulcer at the site of the primary lesion. This ulcer was biopsied and showed no tumor. It persisted for approximately 1½ years, when it began to heal. He experienced intermittent major pain during this time. (*C*) At 20 months, the soft tissue necrosis of the tongue had healed, but a bone exposure (*arrow*) had appeared in the left molar gingiva. (*D*) At 2 years, the bone exposure (*arrows*) had increased to 2 cm in length. (*E*) A submandibular abscess developed in association with the gingival necrosis. The patient was experiencing major discomfort, and a resection of the involved mandible was done. (*F*) There was complete relief of pain after resection of the osteoradionecrosis. Patient returned 4 years later with a second large primary lesion of the epiglottis; because of his poor general health, only palliation could be offered. He died of the second primary cancer of the epiglottis.

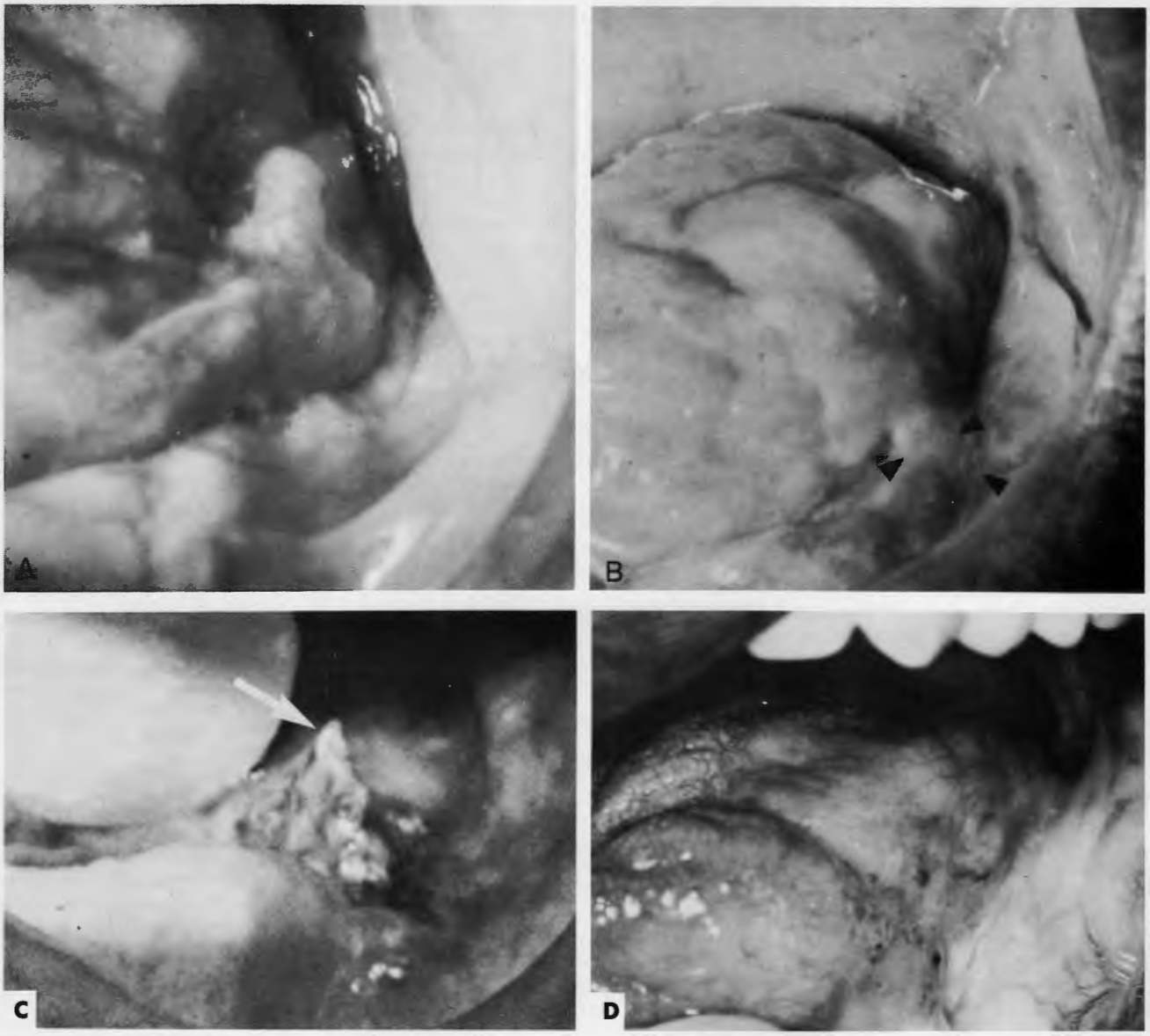


Figure 16-50. (*A*) A 57-year-old man presented with a 1.0 × 1.5-cm ulcerative lesion of the lateral border of the oral tongue (T1N0). In November 1968, the patient was treated with 3000-cGy tumor dose over 2 weeks through a single left lateral field that included the submaxillary and subdigastric lymph nodes, followed by a single-plane radium implant to the tongue delivering 5000 cGy to 0.5 cm. No packing was placed between the gingiva and tongue. (*B*) Acute radiation mucositis was noted 3 weeks after radium needle implant. Note the small patch of mucositis extending to adjacent gingiva (*arrowheads*). Complete healing was noted at 6 weeks. In January 1970, there was a 1-cm superficial ulceration on the surface of the tongue, which healed in 1 month. The patient was wearing his dentures all the time. In February 1971, a 2-mm, asymptomatic ulcer appeared on the left mandible with bone exposed. In May 1972, the bone exposure had increased in size but was still asymptomatic. Six years after therapy, there was a 4 × 12-mm area of bone exposure but the patient was still asymptomatic. (*C*) The bone exposure remained stable until May 1978 (9½ years), when it was noted to have increased in size to 1.0 × 1.5 cm with a sequestrum (*arrow*) projecting about 1 cm above the gingiva. (*D*) The sequestrum separated spontaneously, and the gingiva completely covered the defect in the gum, as shown in this photograph of January 1982. The patient remained alive and free of disease at 14 years.

quently it is "not as keen" as before. The dryness of the mouth may contribute to the poorer sense of taste.

Return of saliva is variable, depending on the treatment volume and the dose to the salivary glands. Patients treated with interstitial therapy alone eventually have nearly normal saliva. Patients treated with 4500 cGy over 5 weeks or 3000 cGy over 2 weeks by external-beam therapy plus interstitial therapy eventually have a modest return of saliva.

SOFT TISSUE NECROSIS. Soft tissue necrosis is fairly common, although frequently of minor degree. Once recurrence has been ruled out, considerable patience is required for healing. The patient associates pain with recurrence of cancer, because the original lesion frequently caused a similar pain. The patient needs to be constantly reassured that the ulcer will heal slowly and that there is no evidence of recurrence. Patients who develop a radiation necrosis uncommonly develop a recurrence, so, in a sense, at least there is some good news associated with the pain (Fig. 16-48). The treatment plan for soft tissue necrosis is mainly to rule out recurrent cancer, to provide local and general analgesia, and to reduce local infection. If the ulcerated lesion has all the earmarks of necrosis, a trial of conservative treatment is instituted. The patient is placed on a biweekly examination schedule, photographs are taken, and precise drawings are made. Broad-spectrum antibiotics (eg, tetracycline, 1 g/day), local anesthesia applied by a cotton-tipped applicator, and analgesics as needed are prescribed. Frequently, pain is reduced dramatically in 1 to 3 days after starting antibiotics, but sometimes there is no response. Lidocaine (Xylocaine Viscous) can be applied to the ulcer with a cotton swab for local analgesia. We have had no success with alcohol nerve blocks. Hyperbaric oxygen treatment may be tried in difficult cases, but it is expensive. We have tried local fulguration with silver nitrate to attempt pain relief but have had little success; we have no experience with cryotherapy.

When all else fails and the necrosis is persistent and the pain uncontrollable, the necrosis must be resected (Fig. 16-49). A flap may be needed to fill the void.

The key word for management of radiation necroses is *patience.*

RADIATION-INDUCED BONE DISEASE. The retromolar trigone and horizontal ramus of the mandible are common sites of radiation-induced bone disease. The ascending ramus of the mandible is uncommonly the site of radiation-induced bone disease. The edentulous patient is less likely to develop serious radiation-induced disease of the mandible than is a patient with teeth.

The mandible may be affected in several ways. The most frequent problem involving the mandible is *bone exposure.* The onset varies from 1 month to many years after completion of radiation therapy. The gingiva and usually the periosteum disappear, exposing the underlying bone. The exposed area or areas usually vary from 2 mm to 2 cm in diameter. There is either minimal pain or modest discomfort, which is usually intermittent. In fact, if the exposed area is small, the patient is often unaware of the problem. The bone often appears intact on roentgenograms. Biopsy is not needed unless there was tumor on the gingiva before treatment. If the patient has dentures, they should be discontinued or, in certain cases, altered by the dentist to relieve the denture over the exposed bone. If sharp bony edges appear, they are filed to a smooth contour and the bone edge is lowered to speed healing. The bone exposure may become more or less stationary at this point. Healing may require months to even years. Healing occurs when the gingiva regrows to cover the exposed area; a small piece of bone may sequestrate first. *Patience* is the major requirement (Fig. 16-50.

In some instances, the bone exposure may progress so that a large area of bone is exposed. Pain is usually intermittent and mild to moderate; occasionally, it is severe. Antibiotics usually reduce pain when it does occur. Local care is similar to that used for early bone exposures. It is amazing that rampant osteomyelitis uncommonly develops in the exposed, relatively avascular bone.

In some cases, the bone becomes frankly necrotic with intermittent sequestration. Hyperbaric oxygen treatment has been used with some success (see Chap. 10). It is a matter of individualization as to when surgical intervention should be instituted. Conservative measures should be given a fair trial, but if pain becomes a problem, an operative procedure must be considered. In advanced cases, the dead bone is removed and covered with a flap carrying its own blood supply.

BUCCAL MUCOSA

Carcinoma of the buccal mucosa is associated with the use of tobacco, particularly snuff and chewing tobacco. The disease is infrequent in the United States. In the southeastern United States, it is usually seen in older women, being more common in women than men in ratio of approximately 3 or 4 to 1.[43]

Anatomy

The buccal mucosa is the mucous membrane covering the inner surface of the cheeks and lips. It ends above and below with a transition to the gingiva. It ends posteriorly at the retromolar trigone. The parotid duct opens into the buccal mucosa opposite the second upper molar. The muscular wall is composed mainly of the orbicularis oris anteriorly and the buccinator muscle posteriorly. The buccinator is covered externally by the buccal fat pad. The masseter muscle lies lateral to the buccinator muscle with its anterior margin opposite the retromolar trigone. The blood supply is a branch of the facial artery. The long buccal nerve, a branch of the mandibular, is sensory to the buccal mucosa and the skin of the cheek, which overlies the buccinator muscle. The facial nerve is the motor nerve to the buccinator muscle.

Imaging of the Normal Anatomy

The upper and lower gingivobuccal sulci are best evaluated by physical examination. On axial and coronal images, they are recognized as those spaces just deep to the insertion of the buccinator muscle (see Figs. 16-11 through 16-13). Important deep relationships of the gingivobuccal sulci include the fat pad of the buccinator space, which is, in turn, contiguous with the retroantral fat within the infratemporal fossa.

Pathology

The majority of malignant tumors are low-grade squamous cell carcinoma, and they frequently appear on a background of leukoplakia. This is a frequent site for

verrucous carcinoma to occur. Verrucous carcinoma may be particularly difficult to diagnose histologically because of associated inflammatory changes. An example of a patient who had multiple biopsies interpreted as pseudoepitheliomatous hyperplasia until the tumor grew through the skin and into the temporal fossa is shown in Figure 16-51. Minor salivary gland tumors are rarely seen and tend to occur on the mucosa of the upper lip.

Patterns of Spread

Almost all of the squamous cell carcinomas originate on the lateral walls and rarely on the wet mucosa of the lips. Early lesions are usually discrete, elevated tumors and are often exophytic. As they enlarge, they penetrate the underlying muscles and eventually penetrate to the skin and infratemporal fossa. Peripheral growth occurs into the gingivobuccal gutters and eventually onto the gingiva and underlying bone. The parotid gland and facial nerve are invaded in advanced lesions.

Squamous cell carcinomas arising from the moist mucosa of the lips are uncommon. The three cases observed were all near the midline of the lower lip and near the gingivolabial sulcus in the area where snuff was held (Fig. 16-52).

The lymphatic spread is first to the submandibular and subdigastric nodes. Contralateral involvement on admission would be unusual. The incidence of positive nodes on admission is 9% to 31%, and the risk of subclinical disease is 16% (see Table 6-2).

Clinical Picture

Early, asymptomatic lesions may be discovered by the dentist or physician. A background of leukoplakia is present in nearly half the patients and is sometimes extensive. Small lesions produce the sensation of a lump that is felt with the tongue. Pain is minimal even when the lesion becomes large, unless there is posterior extension to involve the lingual and dental nerves. Pain may be referred to the ear. Obstruction of Stensen's duct may produce parotid enlargement. Extension posteriorly behind the pterygomandibular raphe into the pterygoid muscles or into the buccinator and masseter muscles eventually causes trismus. Intermittent bleeding occurs when the lesion is irritated by chewing or is ulcerated by growing against the teeth. Multiple lesions may be present (Fig. 16-53).

Methods of Diagnosis and Staging

The differential diagnosis includes leukoplakia, candidiasis, and lichen planus; lues and tuberculosis are rarely seen today.

If the first biopsy report is chronic inflammation or pseudoepitheliomatous hyperplasia and there is an obvious neoplasm present, repeat biopsy is in order. Multiple repeat biopsies are often required to establish the diagnosis, and the physician must be skeptical of a benign diagnosis in the face of an obvious neoplasm that is enlarging and not responding to conservative management.

Diagnostic Imaging

Many lesions of the buccal mucosa do not come to imaging. The ones that do are usually locally advanced and studied mainly because of uncertainty relative to the deep extent of the lesion or bone invasion. Methods for evaluating the mandible are discussed in detail in the previous section on the floor of the mouth. These are applicable to the maxilla and the maxillary alveolar ridge as well.

Spread toward the hard palate, maxillary antrum, and nose is best imaged in the coronal plane and primarily by CT because bone destruction is often an important finding. (See the section in this chapter on diagnostic imaging for the retromolar trigone for posterolateral spread to the retromolar area.) Soft-tissue spread laterally may see the lesion penetrate the buccinator and go on to involve the buccal fat pad with continued spread to the masseter, pterygoid, and, if high enough, temporalis muscles. Continued spread along these muscles can lead to mandibular invasion, usually in and about the region of the coronoid process or ascending ramus anteriorly. Lesions that involve the lower gum may invade the mandible along zones of dehiscent periosteum adjacent to teeth. Slow-growing lesions adjacent to the mandible may occasionally cause saucerized defects in the bone. If the lesions reach the pterygomandibular raphe, the spread pattern is much as in retromolar trigone cancer.

Advanced cancers may extend into the soft tissues of the cheek, and it might be difficult to separate primary tumor from involvement of lymph nodes.

Imaging of the lymph nodes is discussed in Chapter 6. The parotid and facial nodes must be included for lesions with deep lateral spread (see Fig. 6-31).

Staging

The AJCC staging system was given at the beginning of this chapter. The thickness of the lesion and the depth of invasion are also important prognostic factors.

Treatment

Selection of Treatment Modality: Primary Site

Small lesions, 1 to 2 cm, not involving the commissure, may be excised with primary closure or mucosal flap; small lesions that involve the oral commissure are best treated by radiation therapy. Lesions that are 2 to 3 cm in size are often treated by radiation therapy (Figs. 16-54 and 16-55); these lesions can be excised and grafted, but the graft tends to shrink and become firm; this makes detection of recurrence difficult, and the lining of the cheek feels tight, rough, and uncomfortable to the patient. More advanced lesions are treated by either radical surgical excision, radiation therapy, or a combination of both on an individual basis. Preference is given to radiation therapy when the tumor invades near the commissure. Preference is given to an operation when there is extension to the gingiva or invasion of the mandible or maxilla.

Management of the Neck

PRIMARY LESION MANAGED BY SURGERY. Elective ipsilateral neck dissection may be done or the neck may be observed, assuming close follow-up. Pa-

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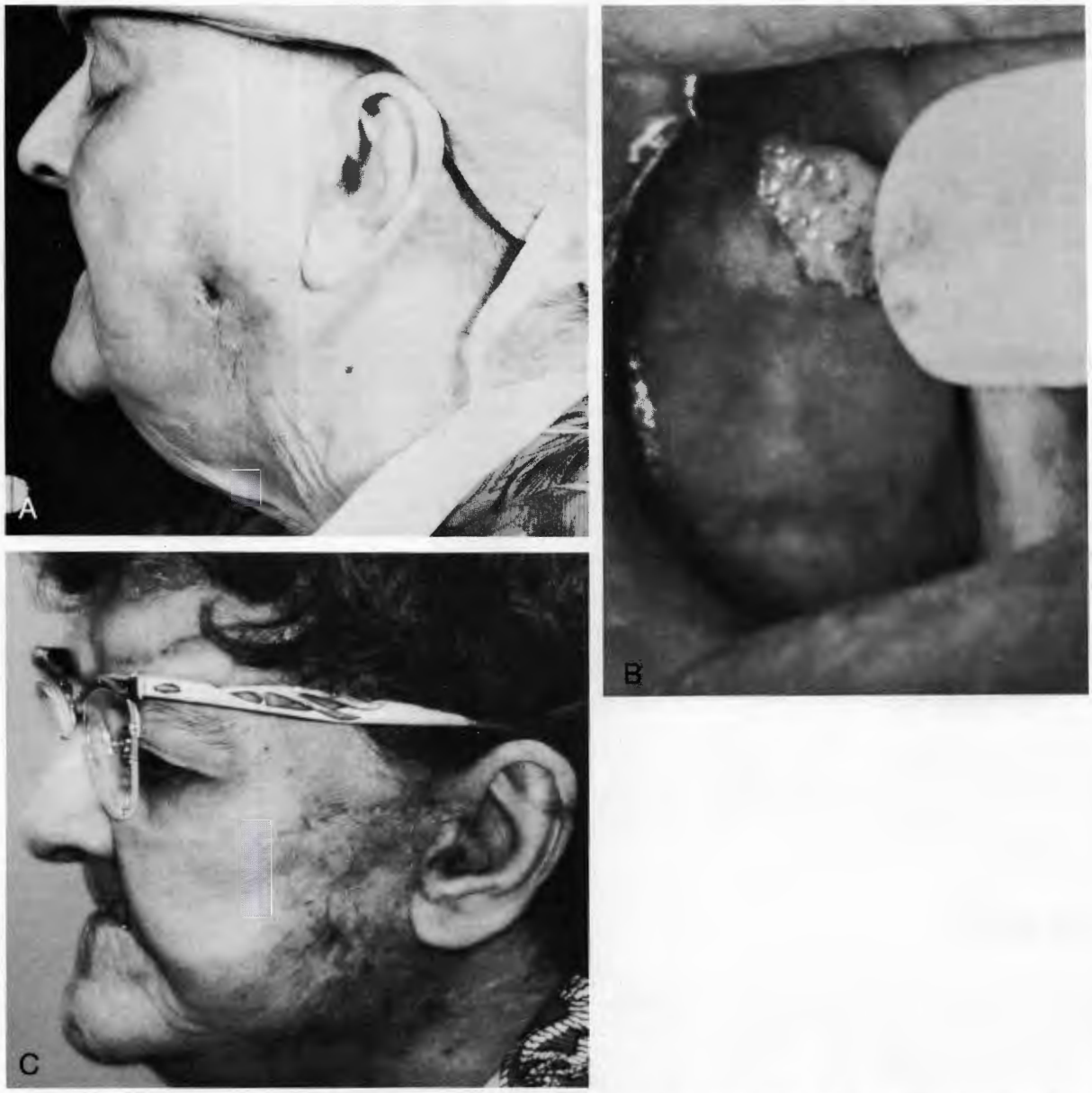


Figure 16-51. Stage IV (T4N0) verrucous carcinoma of the buccal mucosa. In August 1968, after a 4-month history of pain in the cheek and spontaneous drainage of purulent material through the skin of the left cheek 10 days before admission, a biopsy was reported as grade I epidermoid carcinoma of the left buccal mucosa. This diagnosis was revised in 1982 to verrucous carcinoma. Multiple previous biopsy specimens had been reported as "pseudoepitheliomatous hyperplasia and chronic inflammation." (*A*) Appearance before treatment. Physical examination revealed a large subcutaneous mass involving the entire left cheek and extending posteriorly to the level of the tragus, into the temporal fossa, and beneath the mandible. There was ulceration of the buccal mucosa near the retromolar trigone. The neck was negative for disease. Roentgenograms of the mandible showed extensive destruction of the body, angle, and ascending ramus. The initial plan was to resect the lesion and repair with a forehead flap, and a flap was prepared for this procedure; however, the lesion proved to be unresectable owing to invasion into the squamous portion of the temporal bone, and radiation therapy was elected. The patient received 5450 cGy tumor dose, ^{60}Co, through superior- and inferior-angled wedge fields. This was followed by a large single-plane radium needle implant for 3500 cGy at 0.5 cm. The findings of multiple biopsies are listed below:

6 months: 2 × 2-cm recurrence on buccal mucosa. Local excision revealed verrucous carcinoma.
1 year: 1.0 × 1.5-cm recurrence on anterior buccal mucosa. Local excision revealed verrucous carcinoma.
3½ years: Granular lesion of retromolar trigone/glossotonsillar sulcus (*B*). Local excision revealed acute and chronic infection, no tumor.
4½ years: Biopsy of retromolar trigone revealed acute and chronic infection, no tumor.
5 years: Biopsy of retromolar trigone revealed hyperkeratosis, no tumor.
8½ years: Biopsy of retromolar trigone revealed hyperkeratosis, no tumor.
9 years: Irregular lesion of retromolar trigone area, 2.5 × 2.5 cm. Biopsy revealed no tumor.

(*C*) Appearance 9 years after initial treatment. Note the marked skin and subcutaneous changes from high-dose irradiation to an advanced lesion. Repeat biopsy at 9½ years showed spindle cell carcinoma. Review of two previous biopsies revealed spindle cell carcinoma to be present in all specimens. At 10 years, chemotherapy was reported to produce a good response. Patient died of cancer at 10½ years.

This case history emphasizes the difficulties faced by the pathologist and treating physician in the management of very low-grade neoplasms. It is a moot point whether the change to a higher-grade lesion is related to the radiation therapy or is the natural history of the disease.

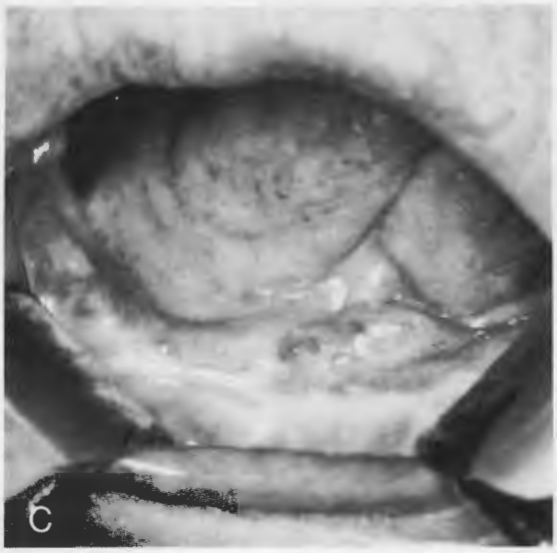


Figure 16-52. (*A*) Squamous cell carcinoma of the wet mucosa of the lower lip. Initial treatment was by radium implant; the carcinoma recurred locally 2 years later and was managed by surgical excision. (*B* and *C*) There was no evidence of cancer 9 years after surgical resection.

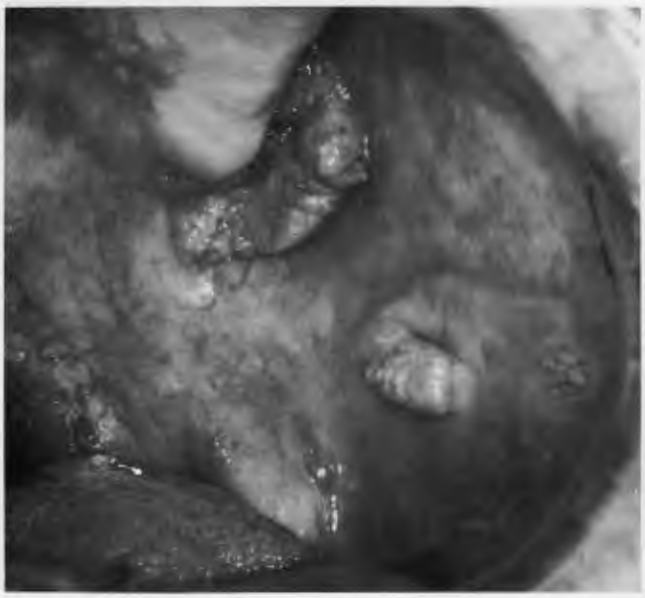


Figure 16-53. Two discrete verrucous carcinomas occurring in a woman who used snuff for many years. There were multiple other areas of leukoplakia and dysplasia throughout the oral cavity. Treatment was by wide local excision.

Figure 16-54. Squamous cell carcinoma of the right buccal mucosa, 3.0 × 2.5 cm (T2N0).

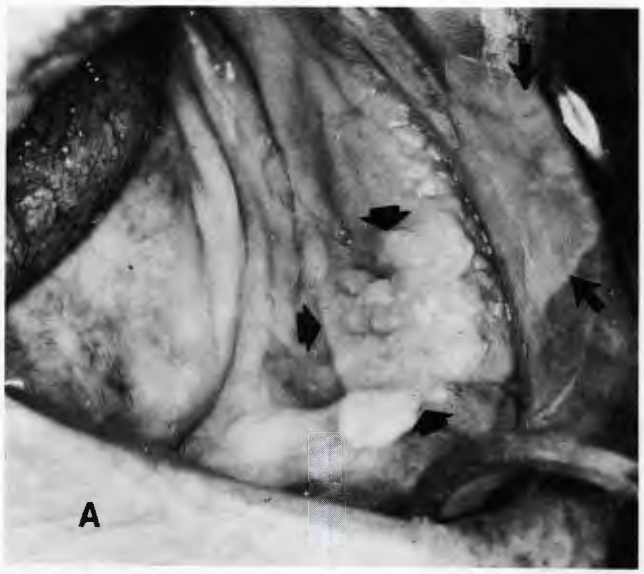


Figure 16-55. An 87-year-old woman had a 2.5 × 3.0-cm squamous cell carcinoma involving the anterior buccal mucosa (*arrowheads*) with extension of filmy leukoplakia (*arrows*) to the commissure of the lip. Treatment was a radium needle implant, 6000 cGy at 0.5 cm. There was complete healing, and the filmy leukoplakia also disappeared. The patient died at 21 months of intercurrent disease.

tients with clinically positive necks are managed according to the guidelines in Chapter 6.

PRIMARY LESION MANAGED BY IRRADIATION. Elective ipsilateral neck irradiation may be given in conjunction with treatment to the primary lesion. (See Chap. 6 for guidelines for the clinically involved neck.)

Surgical Treatment

Lesions that invade the mandible or maxilla require that an appropriate amount of bone be resected along with the soft tissues. Repair may require a maxillary prosthesis. Full-thickness removal of the cheek is repaired by a myocutaneous flap.

Irradiation Technique

The primary lesion and first-echelon lymph nodes are included in the external-beam portal. An ipsilateral portal of electrons or mixed beams is usually selected. A lead block placed in the mouth helps decrease irradiation of the opposite side. A wedge pair is appropriate for some situations. A portion of the treatment is given with intraoral cone, or interstitial techniques when possible. Part of the upper and lower lips may be sutured together if the implant includes the lip commissure. When tumor extends into one of the gingivobuccal gutters or onto gingiva, treatment is entirely by external-beam irradiation; an intraoral cone may be used if possible. There are no data on the dose required for control, but dose schedules similar to those recommended for floor of mouth can be adopted. The cheek and facial nerve are tolerant of high doses. Marginal failures occur, and the initial treatment area should be a bit more generous than for lesions of comparable size in other sites.

Management of Recurrence

Surgical failures are managed by surgery, radiation therapy, or both. Radiation therapy failures are managed by resection and repair with a flap. Local excision with primary closure or split-thickness skin graft is usually not possible for radiation therapy failures.

Results of Treatment

Ash[5] reported 35% absolute 5-year survival for 374 patients with carcinoma of the buccal mucosa for all stages. The initial treatment to the primary lesion was radiation therapy in 97% of the patients. The primary lesion was initially controlled in 53% of patients with early lesions and 25% with advanced lesions; salvage raised the ultimate control rates to 69% and 34%, respectively.

TABLE 16-24. Carcinoma of the Buccal Mucosa: Surgical Results—Distribution of Clinical Factors and Rates of Recurrence

Clinical Factors*	Patients	Recurrence
GENDER		
Male	12	6 (50%)
Female	77	22 (29%)
AGE		
<70 y	36	12 (33%)
>70 y	53	16 (30%)
CLINICAL STAGE		
I	22	4 (18%)
II	30	10 (33%)
III	20	6 (30%)
IV	17	8 (47%)
TUMOR STAGE		
T1	23	5 (22%)
T2	32	11 (34%)
T3	20	6 (30%)
T4	14	6 (43%)
THICKNESS*		
<3 mm	18	4 (22%)
3–5.9 mm	26	6 (23%)
>6 mm	26	14 (54%)
DEPTH OF INVASION*		
<1 mm	13	2 (15%)
1–2.9 mm	18	6 (33%)
>3 mm	22	12 (54%)
TOTAL CASES	89	28 (31%)

* $P < .01$.

(Urist MM, O'Brien CJ, Soong SJ, Visscher DW, Maddox WA. Squamous cell carcinoma of the buccal mucosa: analysis of prognostic factors. Am J Surg 1987;154:412)

MacComb and coworkers[35] reported the results for 115 patients treated between 1947 and 1962. Irradiation was the initial treatment in 69 patients, surgery was used in 44 patients, and combined therapy was used in 2 patients. The local recurrence rate was 10% for stage I, 12% for stages II and III, and 38% for stage IV. The 3-year absolute survival rate was 49%, and the 5-year absolute survival rate was 48%. The cause-specific 3- and 5-year survival rates were 71% and 70%, respectively. The same authors reported a 35% cure rate for 40 patients referred after failure of initial treatment given elsewhere.

Urist and associates[78] reviewed the results for 89 patients with 105 squamous cell carcinomas of the buccal mucosa treated by surgical excision and therapeutic node dissection between 1959 and 1985. The rate of recurrence is related to various clinical factors in Table 16-24. In a multivariate analysis, only tumor thickness greater than 6 mm was a significant prognostic finding. Depth of invasion greater than 3 mm was highly significant as an univariate prognostic finding. The 5-year survival rate by stage was as follows: stage I, 95%; stages II and III, 80%; and stage IV, 55%.

Follow-Up Policy

Patients who have been treated by surgical excision and split-thickness skin graft are difficult to evaluate for recurrence because the graft contracts and makes interpretation of physical findings difficult. Recurrence at the surgical margin is a common site of failures.

Complications of Treatment

The buccal mucosa is tolerant of high-dose radiation therapy, and complications are uncommon. Bone exposure may appear on the mandible or maxilla. Trismus may develop if the muscles of mastication receive high doses in advanced cases. Surgical injury of Stensen's duct may cause obstruction and parotitis; the parotid gland eventually atrophies. The facial nerve is at risk in resection of advanced cases.

GINGIVA, RETROMOLAR TRIGONE, AND HARD PALATE

Carcinomas arising from the upper and lower gingiva have a similar clinical picture and require a similar approach to diagnosis and management. Primary squamous cell carcinoma of the hard palate is uncommon; the majority of hard palate neoplasms are minor salivary gland tumors (see Chap. 28). Some authors include the retromolar trigone with the anterior tonsillar pillar, but the anatomic relationships, natural history, and management are closer to those of lesions of the lower gingiva.

Anatomy

The lower gingiva includes the mucosa covering the mandible from the gingivobuccal gutter to the origin of the mobile mucosa on the floor of the mouth.

There are no minor salivary glands in the "mucous" membrane over the alveolar ridges.

Behind the third molar is a small triangular surface covering the ascending ramus that is called the retromolar trigone; it is continuous above with the maxillary tuberosity.

Beneath the mucosa of the retromolar trigone is the tendinous pterygomandibular raphe, which is attached to the pterygoid hamulus and the posterior mylohyoid ridge of the mandible and serves as the insertion for the buccinator, orbicular oris, and superior constrictor muscles. The pterygomandibular raphe is a dense band of connective tissue that serves as the attachment of the superior constrictor and buccinator muscles. The raphe extends from approximately the level of the posterior edge of the mylohyoid muscle cephalad along the medial aspect of the mandible and continues to the hamulus of the medial pterygoid plate. These deep relationships place the retromolar trigone and pterygomandibular raphe region at the crossroads between the oral cavity, oropharynx, nasopharynx, and floor of the mouth. Just behind the pterygomandibular raphe and between the medial pterygoid muscle and the ascending ramus is the pterygomandibular space, which contains the lingual and dental nerves. The pterygomandibular space is related posteriorly and medially to the contents of the parapharyngeal space.

There is a small fat pad between the pterygoid muscle group and the mandibular foramen through which the mandibular nerve passes before it enters the alveolar canal. The more proximal course of the third division of the trigeminal nerve takes it posteriorly and just medial to the lateral pterygoid muscle group; it continues cephalad just within the fascia of the masticator space to enter the foramen ovale. An approximately 1-cm segment of this nerve is immediately adjacent to the parapharyngeal space before it enters the foramen ovale.

Imaging of the Normal Anatomy

The hard palate is best studied in the coronal plane (Fig. 16-56) and can also be studied with software such as DentaView. The greater and lesser palatine foramina and the neurovascular bundles that run through these foramina to converge in the region of pterygopalatine fossa are best seen on axial sections. Complete study of hard palate cancers requires both planes. Lesions involving the retromolar trigone are usually studied with axial images (see Figs. 16-11 and 16-12). The pterygomandibular space lies just posterior and medial to the pterygomandibular raphe. This small triangular fat pad lies between the medial pterygoid muscle and mandible; it is continuous with the parapharyngeal space and contains the lingual nerve.

Imaging of the mandible is covered in the section on the floor of the mouth.

Pathology

The majority of neoplasms of the gingiva are squamous cell carcinoma. Verrucous lesions occur, usually on the lower gingiva. Melanoma is reported. Metastatic lesions to the underlying bone may be confused with primary tumors.

Epidermoid carcinoma may arise within the body of the mandible or maxilla (intraalveolar epidermoid carcinoma) either from odontogenic epithelium or from epithelium trapped during embryonic development. It is

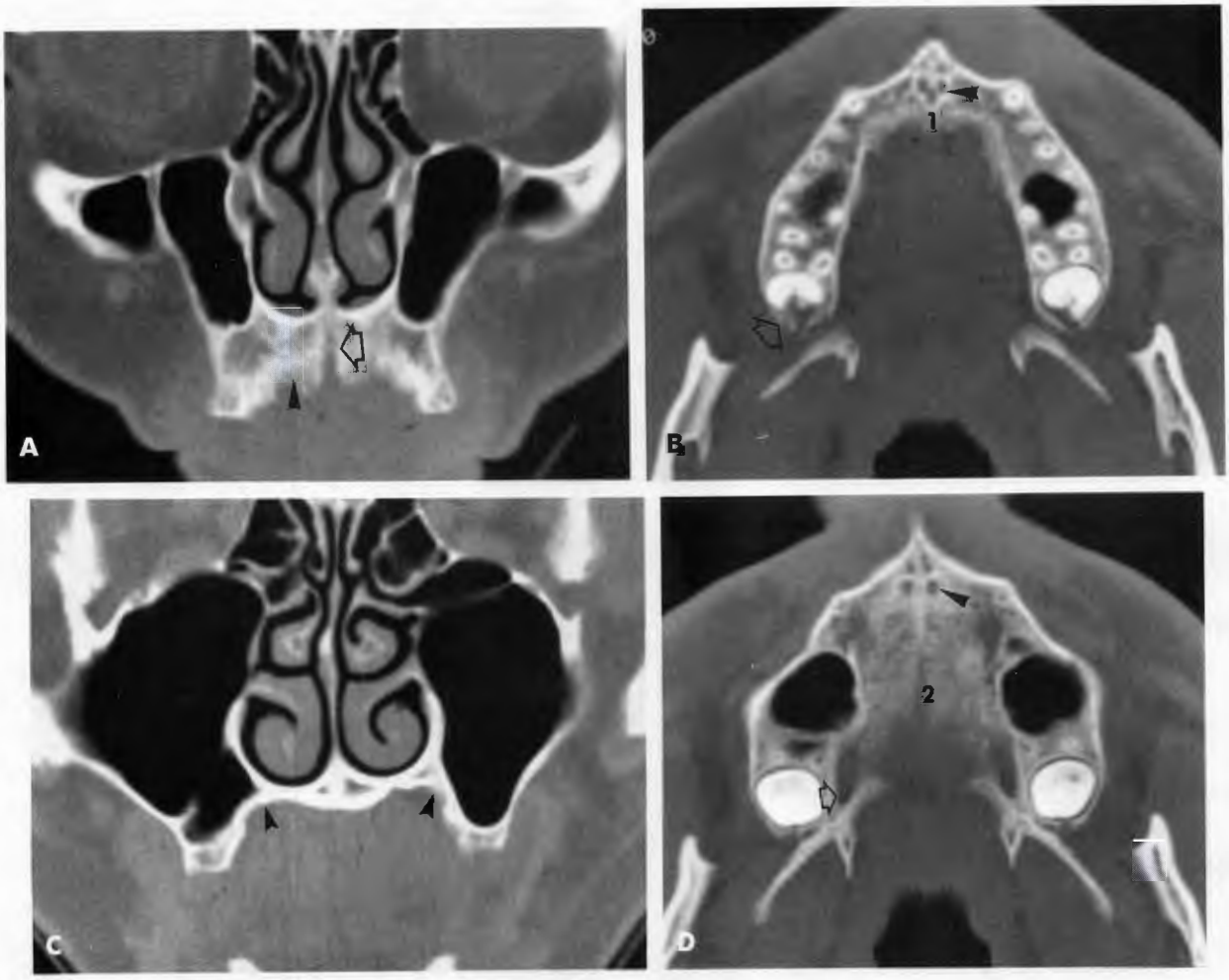


Figure 16-56. Normal CT anatomy of the hard palate. (*A*) Coronal section through the anterior portion of the hard palate. Open arrow points to the incisive canal. This section is made at the junction of the premaxilla and hard palate so that the inferior margin appears somewhat indistinct (*arrowhead*). Slight mucosal thickening along the floor of the nose is a normal variant. (*B*) Axial CT at the junction of the hard palate and maxillary alveolar ridge. The incisive canal (*arrowhead*) is visible within the premaxilla. Note the relation between the maxillary tuberosity (*open arrow*) and the lower pterygoid plates. The number 1 indicates the approximate position of the coronal section shown in *A*. (*C*) Coronal section through the mid hard palate shows how the thickness and slope of the palate can vary depending on the status of dentition or variation in maxillary sinus development. Notice that although there is asymmetry of the bony hard palate contour (*arrowheads*), its cortical margin is intact. These types of variation are common and sometimes cannot be distinguished from pressure-induced remodeling adjacent to a slow-growing tumor. Frank bone erosion is easy to recognize on coronal sections through the palate. (*D*) Axial section made slightly oblique to the plane of the hard palate, causing it to appear indistinct posteriorly. This is frequently the case with axilla sections, and it is essential to study the hard palate with coronal imaging to detect subtle involvement by tumor and other pathology. The uppermost portions of the incisive canals are visible anteriorly (*arrowhead*). The greater palatine foramina are just becoming visible (*open arrowhead*). The number 2 indicates the approximate position of the coronal CT slice seen in *C*. (*E*) Coronal section made at the junction of the hard and soft palate. The greater palatine foramen is visible (*arrowheads*), and it leads to the fat pad within the pterygopalatine fossa (*open arrow*). Note the proximity of the pterygopalatine fossa to the foramen rotundum (*arrow*). (*F*) Axial section through the upper hard palate. Air within the floor of the nasal cavity is vaguely visible on either side of midline (NC). The maxillary spine (*arrowhead*) is visible anteriorly. The greater palatine foramen is now clearly visible as a rounded canal (*open arrow*). The number 3 indicates the approximate position of the coronal section seen in *E*.

more frequent in the mandible than the maxilla and is most common in the molar regions. It must be distinguished from metastatic squamous cell carcinoma and ameloblastoma.

Ameloblastoma is a rare tumor with an incidence of about 1% of all tumors of the maxilla and mandible. Most patients are in the age range of 20 to 50 years. Eighty percent of these tumors occur in the mandible, with the molar regions most commonly involved. No appreciable differences are found by sex or race.[73]

Histologically, the ameloblastoma is an epithelial tumor. The epithelium forms sheets or islands, and the

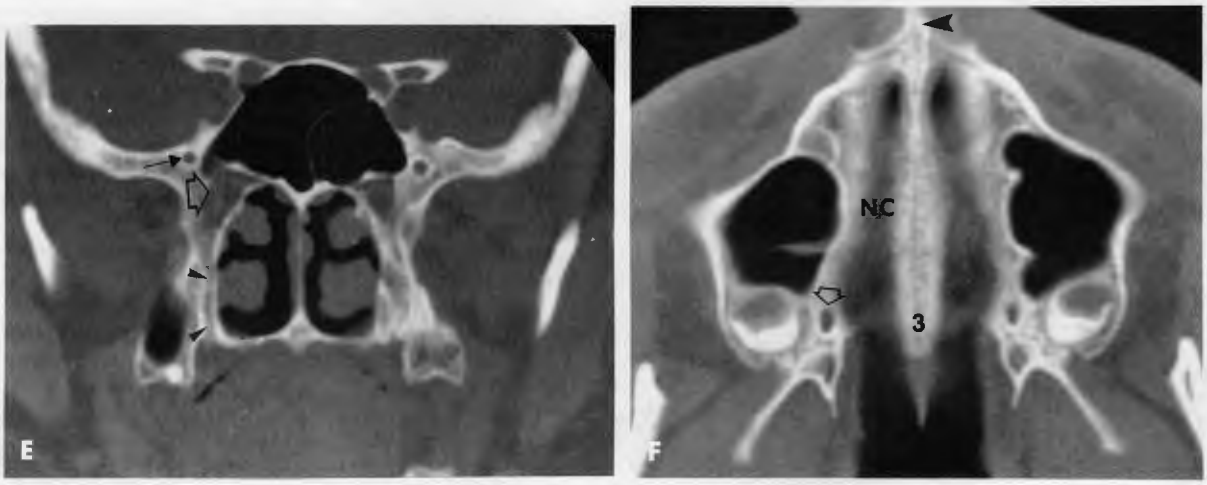


Figure 16-56. ***(Continued)***

peripheral layer is formed by atypical columnar cells.[72] The lesion may appear histologically benign, but it is expansive, tends to recur locally, and may produce distant metastases.[57] Ameloblastoma is histologically similar to basal cell carcinoma.

Malignant tumors of the hard palate are most often minor salivary gland carcinomas, adenoid cystic and mucoepidermoid. Squamous cell carcinoma is relatively uncommon. The hard palate is a common site for the origin of Kaposi's sarcoma.

Patterns of Spread

Lower Gum

Squamous cell carcinomas invade the periosteum, mandible, retromolar trigone, adjacent buccal mucosa, and floor of the mouth. Slow-growing lesions tend to produce atrophy of adjacent bone and cause a smooth, saucerized defect before invading the mandible. Other lesions invade the bone directly.

Byers and associates[11] reported that 23% had associated leukoplakia, 36% had mandible invasion, and 5% had perineural involvement.

Squamous cell carcinoma usually invades the medullary cavity of the mandible through the occlusal surface (alveolar ridge) because there is no complete bony barrier in the edentulous portion of the mandible. The lingual and buccal plates are relatively resistant to tumor penetration. Entry through the mental, mandibular, genial, and other small foramina occurred in only 8% of cases studied by McGregor and MacDonald.[42] In the previously irradiated mandible, tumor entry into the mandible occurred at more varied sites, but the occlusal surface was still the most common.

The patterns of spread of squamous cell carcinoma within the mandible were studied by whole-organ sections in 39 specimens cut in cross section at 4- to 5-mm intervals. Two modes of spread were seen: spread in relation to the inferior alveolar nerve and spread between bony trabeculae. Nerve-related spread (perineural or endoneural) occurred in 42% of edentulous and 10% of partially dentate mandibles. The vertical height of the occlusal ridge above the mandibular canal is reduced in edentulous mandibles so that the neurovascular bundle lies progressively closer to the occlusal surface and is more readily accessible to tumor spread. Skip lesions along the nerve were not seen in this study but have been reported by others. Spread of cancer from the perineural spaces into the medullary bone was not seen. Nerve-related spread is almost always associated with extensive carcinoma in the adjacent medullary bone. Extension of tumor along the nerve beyond the extent of medullary tumor is infrequent, and in no instance was tumor found beyond the intraosseous portion of the nerve. It is virtually impossible to exclude nerve-related spread on clinical or imaging grounds; however, it can sometimes be detected by imaging studies when not suspected clinically.

The limits of tumor spread within the medullary canal correlate closely with the extent of tumor on the occlusal surface. Spread along the medullary canal beyond the normal occlusal mucosa is uncommon and was never observed more than 5 mm beyond the overlying mass. Therefore, resection of the mandible can be estimated on the basis of visible tumor on the occlusal surface.[42] Clinical information can be combined with data from plain radiography and CT to improve the confidence level of the surgical decision, but MRI is not recommended as a routine diagnostic aid for this purpose.

Lymphatic spread is first to the submandibular and upper jugular lymph nodes. Byers and associates[11] reported 16% clinically positive nodes on admission; 13% subsequently showed ipsilateral positive lymph nodes for a total risk of 29%. Contralateral lymph node involvement was found in only 2 of 61 cases reported. Subclinical disease has been reported in 17% to 19% (see Table 6-2). The distribution of involved nodes after elective neck dissection for carcinomas of the lower gum are shown in Figure 16-57. The incidence of involved lymph nodes was 12% for T1 and T2 and 13% for T3 and T4 lesions. Unusual node groups, including the buccinator, facial, and infraorbital, may be involved.

Upper Gum and Hard Palate

Most of the squamous carcinomas originate on the gingiva and spread secondarily to the hard palate, soft palate, buccal mucosa, and underlying bone; the maxillary antrum may be invaded. Primary carcinoma originating in the maxillary antrum must be excluded because it frequently presents in the upper gum and hard palate. Perineural spread occurs by way of greater and lesser palatine foramina. The risk for positive lymph nodes is 13% to 24% on admission, and the incidence of subclinical disease is 22% (see Table 6-2 and Chap. 28).

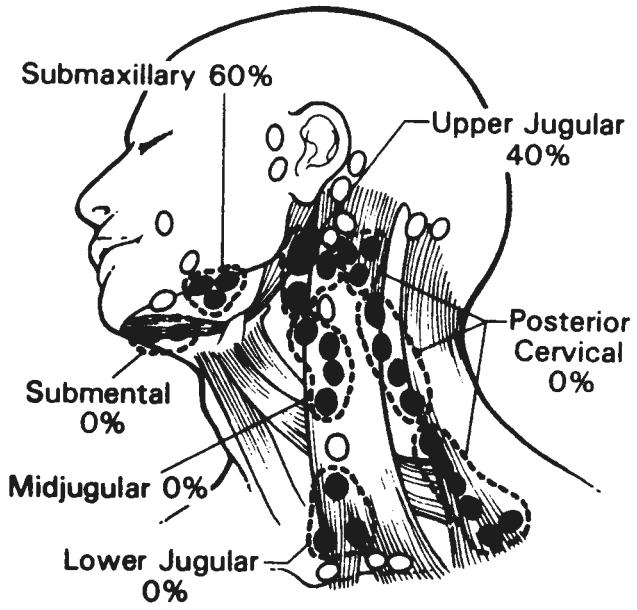


Figure 16-57. Carcinoma of the lower gum. The distribution of involved lymph nodes after elective modified neck dissection for patients with a clinically negative neck. (Byers RM, Wolf PF, Ballantyne AJ. Rationale for elective modified neck dissection. Head Neck Surg 1988;10:163)

Retromolar Trigone

The retromolar trigone is a small area; spread to adjacent buccal mucosa, anterior tonsillar pillar, lower gum, and maxilla occurs early. Posterior spread occurs early into the pterygomandibular space and the medial pterygoid muscle. Posterolateral spread occurs into the buccinator muscle and fat pad. Invasion of the periosteum of the mandible occurs early, but invasion of the underlying mandible tends to be a late manifestation. The cortex of the mandible is dense, which explains the infrequent bone invasion in the region of the retromolar trigone. Byers and coworkers[10] reported a 25% incidence of pathologically proven bone invasion for 60 operated cases. Superior spread along the pterygomandibular raphe as high as the maxillary tubercule is usually easy to see and palpate. When tumor spreads to this level, continued spread to the pterygoid plates or retroantral fat pad is possible. From here, tumor may involve the posteroinferior alveolar neurovascular bundles and permeate the back wall of the maxillary antrum. Continued cephalad growth within the retroantral fat pad or along these neurovascular structures may direct tumor to the pterygopalatine fossa, skull base, and even the cavernous sinus.

The submandibular and subdigastric lymph nodes are the first-echelon lymph nodes. The incidence of clinically positive ipsilateral nodes on presentation is 39%,[10] and the risk for subclinical disease is about 25% (see Table 6-2).[13] The distribution of involved lymph nodes after elective neck dissection for 23 patients is shown in Figure 16-58. The nodal distribution on admission for 227 patients with carcinoma of the retromolar trigone/anterior tonsillar pillar is shown in Figure 16-59.[34] The lymphatic spread patterns for the anterior tonsillar pillar and the retromolar trigone are similar. A few cases have been seen and documented of spread to facial and retrozygomatic nodes (see Fig. 6-34).

Ameloblastoma

Ameloblastoma is a rather indolent tumor that destroys bone and slowly extends to adjacent areas by continuous growth. Regional and even distant metastasis may occur in a few cases, but, even when present, it may be compatible with a long natural course. Metastatic disease usually appears in the lungs; bone and liver metastases have been reported.[68]

Clinical Picture

The patient with squamous cell carcinoma of the gingiva and hard palate may present first to the dentist with either ill-fitting dentures, dental pain, loose teeth, or a sore that will not heal. A history of inappropriate dental extractions or root canal therapy is common. Intermittent bleeding and mild pain occur when the lesion is traumatized. Involvement of the inferior dental nerve may produce paresthesias or anesthesia of the lower lip. A background of leukoplakia is frequently present. The differential diagnosis includes denture sore, dental abscess, granuloma, papilloma, and underlying bony cyst or tumor originating in bone, including metastatic tumor.

Retromolar trigone lesions produce local pain and pain referred to the external auditory canal and preauricular area (see Fig. 16-16). Invasion of the pterygoid muscle produces trismus, usually accompanied by severe pain. Invasion of the underlying mandible occurs in the advanced lesion, but small lesions usually show only periosteal invasion.

Intraalveolar epidermoid carcinoma usually presents with dental symptoms. A submucosal mass is palpable adjacent to the lytic lesion in the mandible. Plain radiographs show a lytic lesion in the mandible.

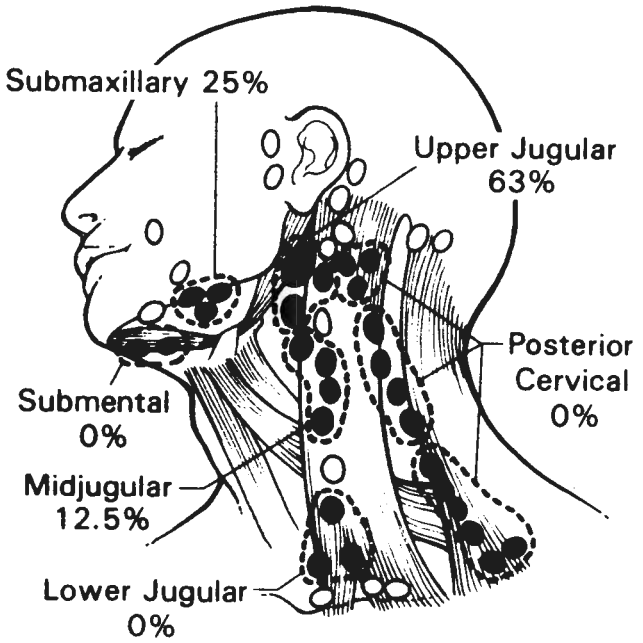
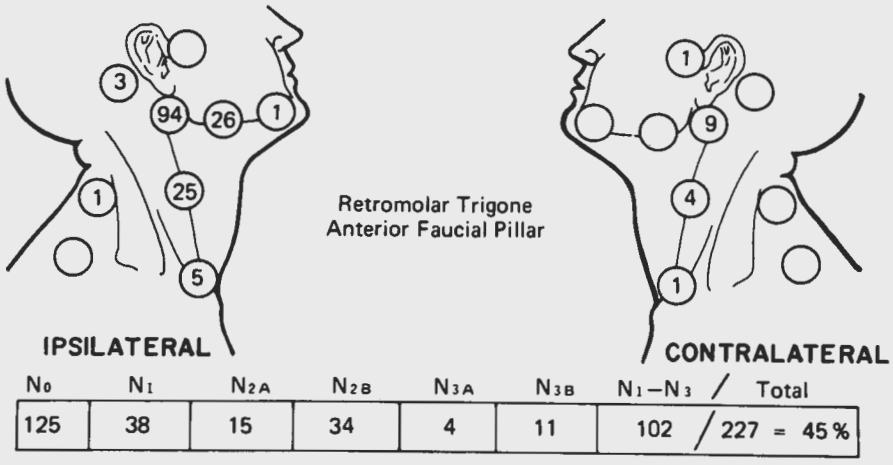


Figure 16-58. Carcinoma of the retromolar trigone. The distribution of involved lymph nodes after elective modified neck dissection for patients with a clinically negative neck. (Byers RM, Wolf PF, Ballantyne AJ. Rationale for elective modified neck dissection. Head Neck Surg 1988;10:163)



N_0	N_1	N_{2A}	N_{2B}	N_{3A}	N_{3B}	N_1–N_3 / Total
125	38	15	34	4	11	102 / 227 = 45%

Figure 16-59. Carcinoma of the retromolar trigone and anterior tonsillar pillar: nodal distribution on admission, MD Anderson Hospital, 1948 to 1965. (Lindberg R. Distribution of cervical lymph node metastases from squamous cell carcinoma of the upper respiratory and digestive tracts. Cancer 1972;29: 448)

Ameloblastoma is a slow-growing neoplasm with few symptoms in the early stages. Patients may notice a gradually increasing facial deformity or loosening of the teeth or denture.[28] On plain radiographs, a radiolucent area is seen with some of the following features: expansion of the overlying cortical plate, a scalloped margin, a multilocular appearance, and resorption of the roots of adjacent teeth.[44]

Methods of Diagnosis and Staging

Diagnostic Imaging

The imaging approach for evaluating mandibular invasion is discussed in the section on the floor of the mouth in this chapter.

CT is recommended because a detailed study of bony structures, surrounding soft tissues, and regional nodes is required. Supplemental, focused MRI is used when more information concerning the soft tissue extent of the lesion or, rarely, perineural spread seems necessary for management decisions.[38]

The mucosal extent of the lesion is best studied by inspection and is often underestimated by both CT and MRI. Imaging should be performed in any retromolar trigone cancer that has visible spread as high as the maxillary tuberosity or evidence of tumor spilling onto the lingual surface of the mandible and floor of the mouth. Patients with trismus should always be studied. Smaller primary mucosal lesions may only require evaluation of the mandible. Study of the regional lymph nodes is included as part of the basic examination of cancers in this region. The growth of retromolar trigone cancers seems to be, at least in part, directed by the muscular attachments to the pterygomandibular raphe. Tumors that have grown cephalad to involve the region of the maxillary tuberosity may continue cephalad deep to the mucosa and into the fat pad posterolateral to the maxillary antrum. Clinically, there is usually some evidence of tumor in the upper gum around the maxillary tuberosity in such cases. From here, tumors may grow either as a bulky mass or en plaque along the posterior wall of the maxillary antrum. Such growth can never be detected by clinical examination (Fig. 16-60). This growth is seen as infiltration of the fat behind the maxillary antrum and as subtle, but definite, irregularities in the bony wall of the antrum. Continued growth along the posteroinferior alveolar neurovascular bundle is possible and is manifested by subtle, but definite, thickening around the neurovascular bundle. The branches of the distal internal maxillary artery, which descend from the region of the pterygopalatine fossa, may appear enlarged and irregularly thickened owing to tumor. It is essential that one carefully compare the neurovascular bundle on the uninvolved side with that on the involved side. Thickening and irregularity along the vascular channels may continue to the pterygopalatine fossa. Whenever such a perineurovascular spread pattern is seen on lower sections, the study must be carried to the level of the pterygopalatine fossa. The pterygopalatine fossa must be carefully compared with the uninvolved side; obliteration of the fat on the involved side is a definite indication of tumor involvement and may herald further spread centrally to the cavernous sinus, even though this may not be visible on imaging studies. Cavernous sinus spread may be asymptomatic.

The portion of the tumor centered around the retromolar trigone may spread posterolaterally to involve the ascending ramus of the mandible and the masseter muscle and even penetrate into the soft tissues of the cheek in advanced cases. Spread medial to the mandible involves the medial pterygoid muscle. There is almost always trismus. Spread to muscles is somewhat easier to recognize on MRI than on CT. Slightly more medial spread of tumor infiltrates the small pterygomandibular space, which contains the lingual and inferior dental nerves. Infiltration of this space may be predictive of involvement of the lingual nerve. Continued medial spread on the lingual surface of the mandible or along the lower margin of the pterygomandibular raphe brings the tumor in contact with the more posterior aspect of the floor of the mouth and the mylohyoid muscle. Spread within the floor of the mouth may be obvious at the point of penetration posteriorly; however, at times, occult spread anteriorly along the attachment of the mylohyoid muscle may be visible on CT or MRI examination and not palpable or visible at clinical examination (Fig. 16-61). Spread patterns in the floor of the mouth were discussed in a prior section.

Cancers of the hard palate are normally studied primarily with CT with occasional supplemental MRI (Fig. 16-62). If the lesion is an adenoid cystic carcinoma, one must be especially careful to search for perineural

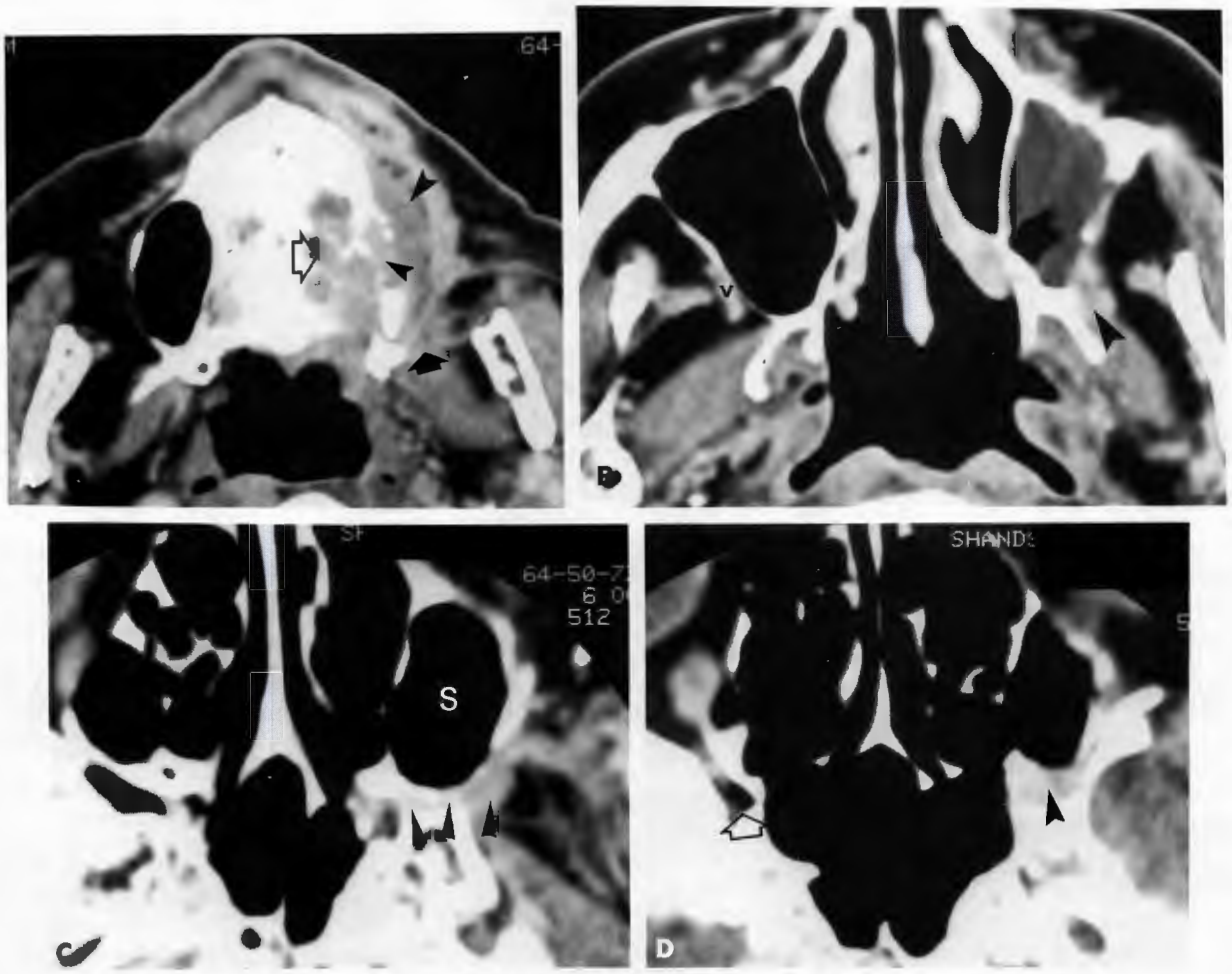


Figure 16-60. A 65-year-old woman had squamous cell carcinoma of the upper gingivobuccal sulcus and alveolar ridge. (*A*) CT section made at the hard palate shows the tumor not only involving the buccal region and alveolar ridge (*arrowheads*), but also extending medially to involve secondarily the hard palate (*open arrow*). Also, note the obliteration of the tissue planes in the upper buccinator space (*arrow*) compared to normal side. (*B*) CT section through the midmaxillary antrum shows continued obliteration of the tissue planes surrounding the distal internal maxillary vessels in the retroantral fat pad (*arrowhead*); compare this to the normal fat pad and maxillary vessels (V) on the opposite side. (*C*) Section through the upper maxillary sinus (S) shows continued thickening of the soft tissues around the distal antral maxillary neurovascular bundle extending into the pterygomaxillary fissure and pterygopalatine fossa (*arrowheads*). (*D*) At the junction of the pterygopalatine fossa and inferior orbital fissure, there is obliteration of the fat within these spaces on the left side (*arrowheads*) as compared with the normal right side (*open arrow*). This spread pattern was unexpected clinically and altered the prognosis and approach to treatment of this patient.

growth along the greater and lesser palatine foramina. Supplemental MRI may be useful in looking for such perineural spread and is also helpful for determining extension into the floor of the nasal cavity or the soft palate.

The neck lymph nodes including the facial and retrozygomatic nodes are studied in all patients who are imaged for the primary cancer. Buccinator node spread has been observed in six cases over the past 8 years (see Fig. 6-31). In rare instances, advanced cancers may extend into the soft tissues of the cheek, and it might be difficult to separate primary tumor from involvement of facial lymph nodes.

Staging

Bone invasion qualifies for T4. Because even small lesions (less than 2 cm) may invade bone, there is a wide prognostic range for T4 tumors.

Treatment

Selection of Treatment Modality: Primary Site

LOWER GUM. The majority of lesions are managed by operation. The surgeon can place no reliance on whether the periosteum can be separated easily from the

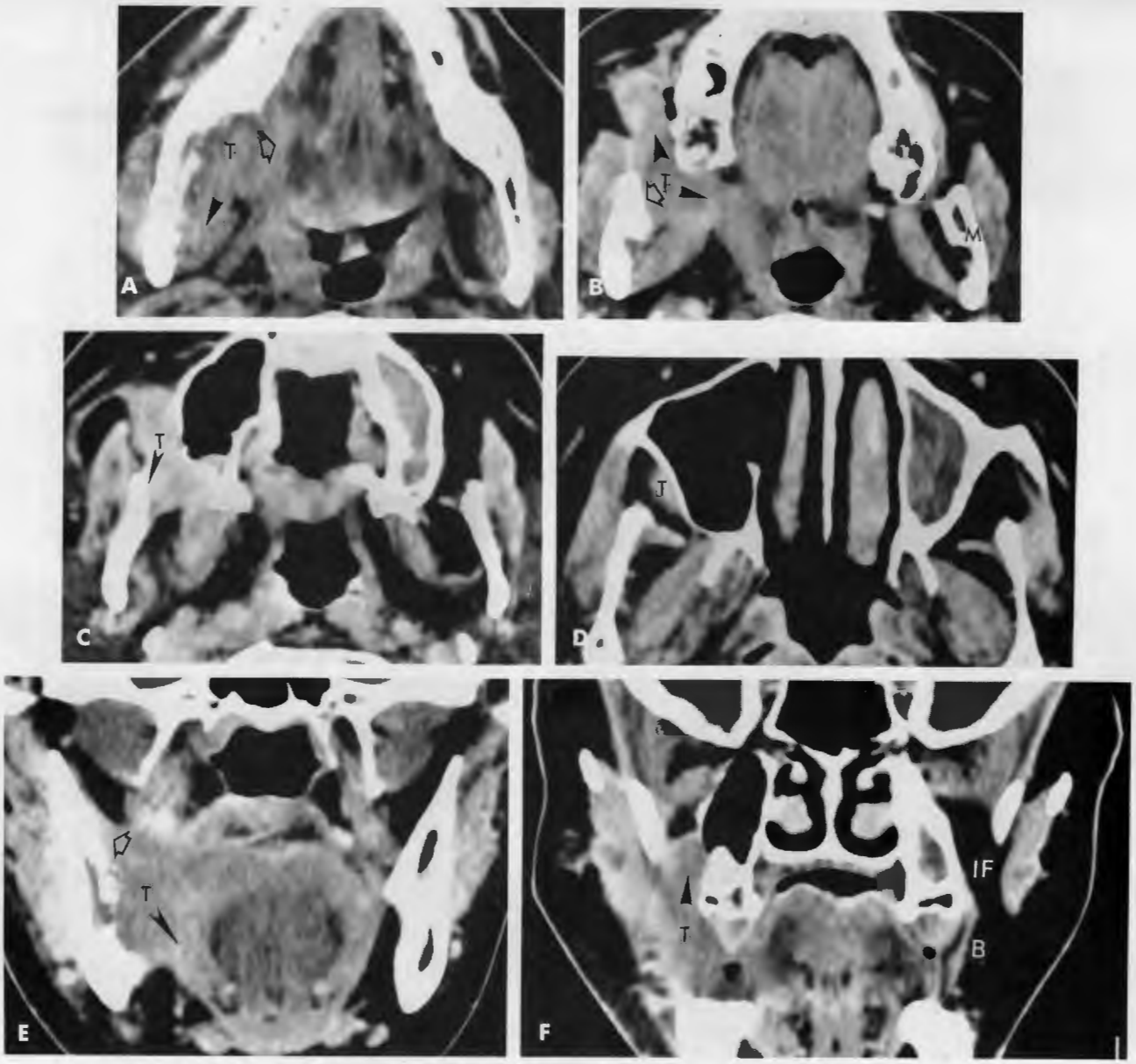


Figure 16-61. Middle-aged woman with advanced squamous cell carcinoma of the retromolar trigone. (*A*) Axial CT at the retromolar trigone level shows tumor (T) destroying the mandible. Soft-tissue margins extend into the posterior aspect of the floor of the mouth (*open arrow*) posteriorly; medially and posterolaterally, tumor involves the medial pterygoid muscle (*arrowhead*) and prestyloid parapharyngeal space. (*B*) Section made at the level of the maxillary tuberosity shows gross tumor (T) spreading anterolaterally into the buccinator space and posteromedially to the junction of the anterior tonsillar pillar and soft palate (*arrowheads*). Maxillary tuberosity is eroded; compare to the normal side. Tumor also extends posterolaterally to spread along the ascending ramus of the mandible (*open arrow*). Note the sclerosis of the mandible and the obliteration of its marrow cavity due to involvement with tumor, compared to the normal mandible (M) on the opposite side. (*C*) Section approximately 1 cm higher than *B* shows continued cephalad spread into the retroantral fat pad and a portion of the infratemporal fossa. Also note continued spread cephalad along the anterior aspect of the ascending ramus of the mandible (*arrowhead*). (*D*) Image approximately 1 cm higher than *C* shows continuous spread of tumor (T) in the retroantral fat pad and portion of the infratemporal fossa. Such occult cephalad spread cannot be anticipated clinically and must be looked for in all cases of advanced retromolar trigone cancer. Partial, posterior maxillectomy will be added to the operative procedure when such extensions are noted on imaging studies. (*E*) Coronal section through the level of the retromolar trigone shows the tumor (T) spreading inferomedially to involve the floor of the mouth (*arrowhead*). The cephalad extension along the ascending ramus of the mandible (*open arrow*) is also easily seen when compared to the normal side. (*F*) Coronal CT section made approximately 1 cm anterior to *E*. Tumor (T) can be seen spreading cephalad within the buccinator space to the infratemporal fossa (*arrowhead*). Note the normal appearance of the buccinator space (B) and its upward extension to become continuous with the low infratemporal fossa (IF) on the normal side.

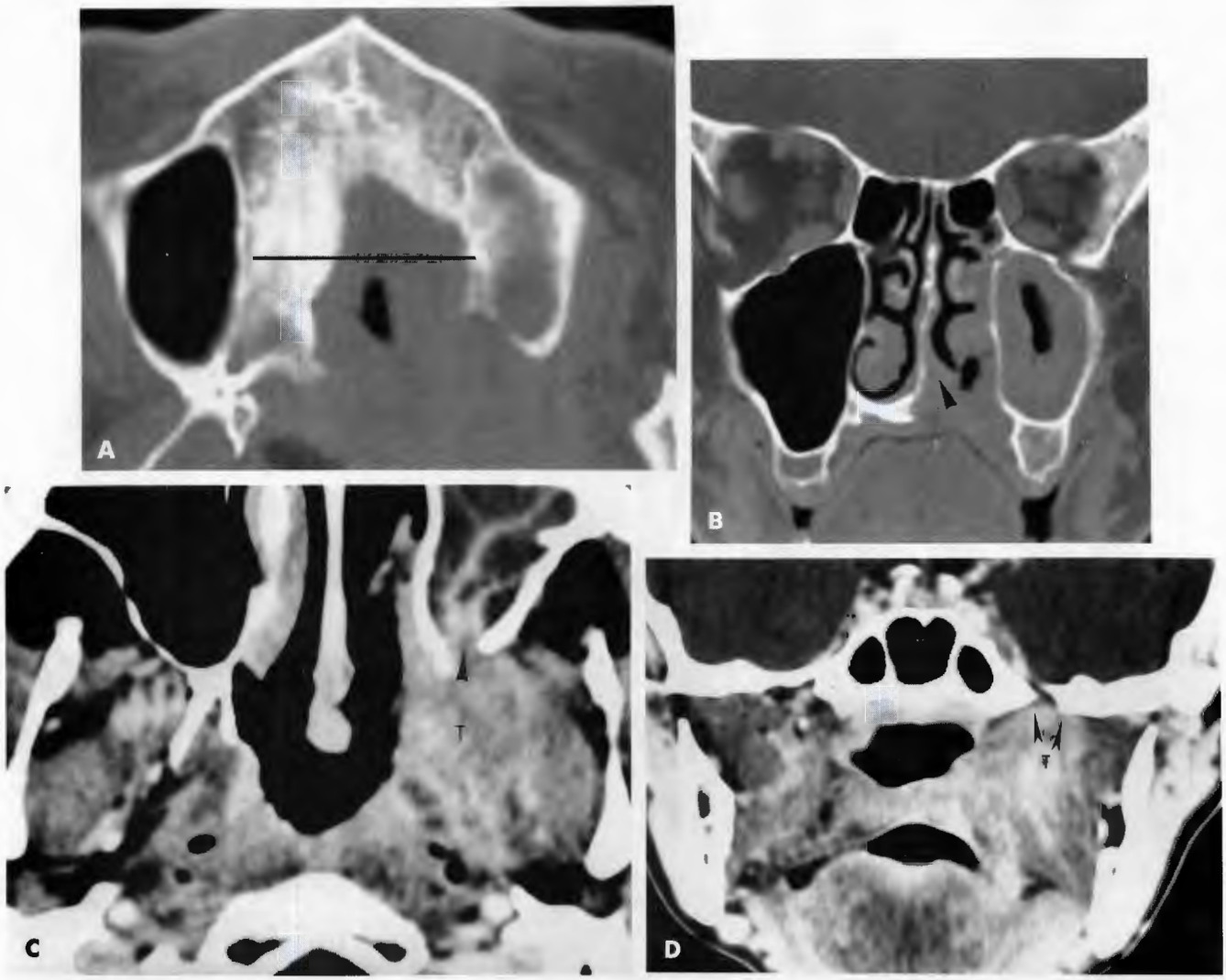


Figure 16-62. A patient who had a lesion that clinically was thought to be a verrucous or very well-differentiated squamous cell carcinoma limited to the hard palate region. (*A*) Axial CT at the level of the hard palate, photographed for bone detail, shows a large defect due to the carcinoma. The horizontal line indicates the approximate position of the coronal section in *B*. (*B*) A coronal section through the posterior aspect of the hard palate shows the left side of the hard palate to be destroyed with tumor extending into the lower portion of the nasal cavity (*arrowhead*). (*C*) Axial section made about 1.5 cm above the hard palate shows extensive, infiltrating tumor within the infratemporal fossa (T) with invasion of the posterior wall of the maxillary sinus. The remainder of the tissue filling the sinus is inflamed, edematous mucosa. (*D*) Coronal section shows that tumor (T) spreading within the infratemporal fossa and parapharyngeal space extended to the skull base in the region of the foramen ovale (*arrowheads*).

bone to guess whether early bone invasion has occurred. Small lesions may be remedied by intraoral resection (with or without a rim resection of bone) and repaired with a split-thickness skin graft. When bone invasion is present or the mandible is enveloped by cancer, removal of a segment of mandible is required. A recent dental extraction in the region of the cancer predicts a higher failure rate, and segmental resection is usually indicated. Large lesions require a hemimandibulectomy. An appropriate elective or therapeutic neck dissection is generally included with segmental mandibulectomy or hemimandibulectomy because the neck is entered to resect the primary lesion. Irradiation may be used for small lesions or for those with only a pressure defect in the bone with good results.

RETROMOLAR TRIGONE. The reported local control rates for T1 and T2 lesions is similar for surgery or irradiation.[10] The major determinant in selection is the status of the teeth. If the patient has an impacted third molar or must have molars removed before radiation therapy, the risk of bone necrosis is substantial and operation is preferred. If the lesion extends to the anterior

tonsillar pillar, soft palate, or buccal mucosa, radiation therapy is selected for the edentulous patient as well as the patient with good teeth (Fig. 16-63). Radiation therapy is less likely to produce a necrosis if an intraoral cone can be used for part of the treatment.

Small retromolar trigone lesions may appear innocuous and easily cured, but they are often more extensive than they seem. Lesions without detectable bone invasion can be resected with a rim or marginal resection of mandible to preserve continuity of the mandible. If rim resection is not feasible, initial treatment with radiation therapy should be considered, with partial mandibulectomy reserved for radiation therapy failure. Large lesions and those with evidence of bone invasion require partial mandibulectomy; approximately two thirds of cases reported by Byers and associates[10] required removal of a segment. Preference is given to surgical treatment for the large lesions unless the cosmetic and functional result would be unacceptable to the patient, in which case operation is reserved for radiation therapy failure. Moderately advanced and advanced lesions are usually managed by resection followed by postoperative radiation therapy.

UPPER GUM AND HARD PALATE. Squamous cell carcinoma on the hard palate and upper gum is relatively rare. Surgical resection is the usual treatment for most small lesions of the upper gum or for extensive bone invasion. Postoperative radiation therapy is added as needed. If the lesion is superficial and extensively involves the hard palate or involves a significant portion of the soft palate with minimal or no bone invasion, radiation therapy is used as the initial treatment. If the lesion is small and discrete and there is no bone involvement, the resection includes the periosteum or occasionally some underlying bone (Fig. 16-64). Bone invasion dic-

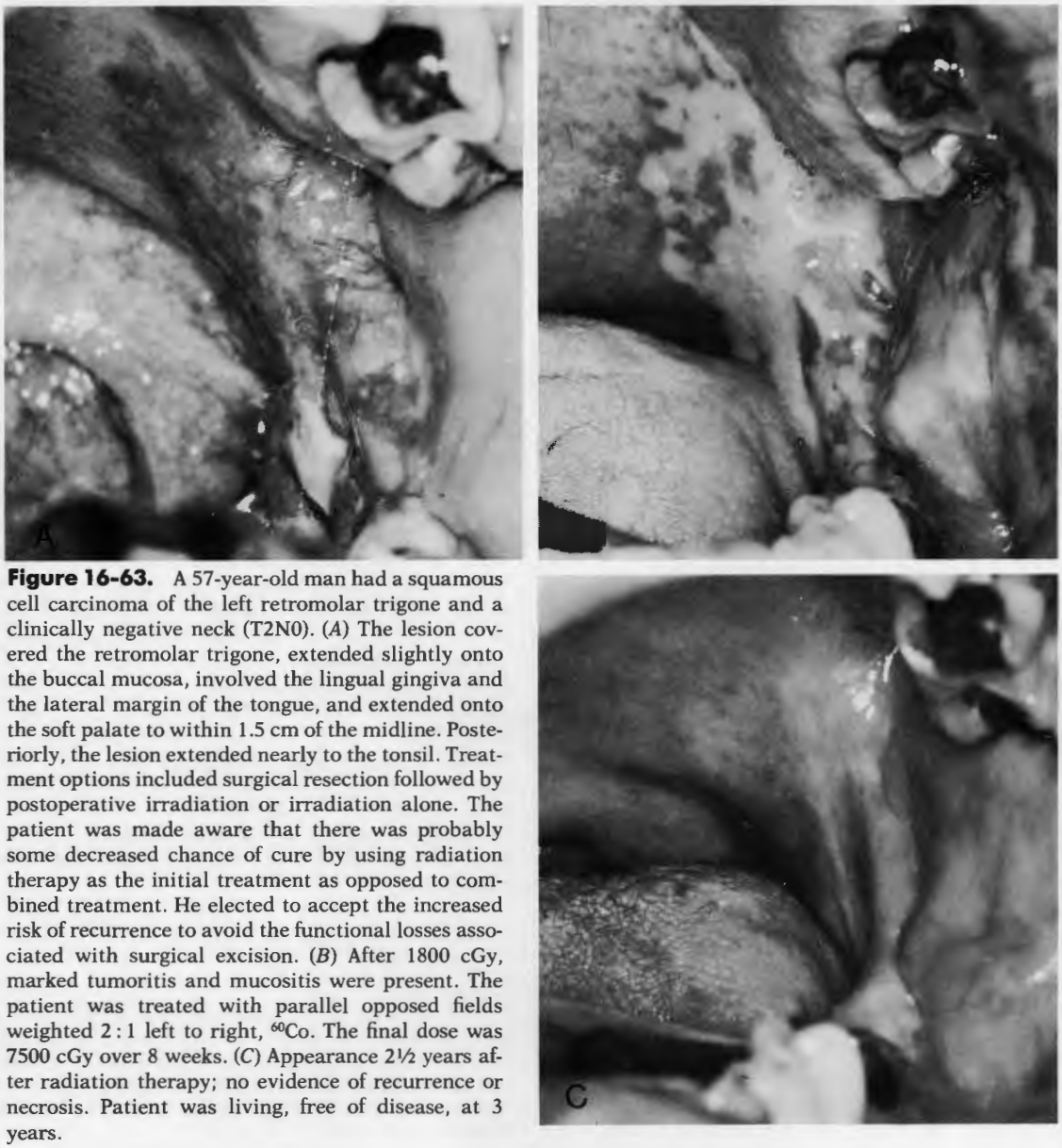


Figure 16-63. A 57-year-old man had a squamous cell carcinoma of the left retromolar trigone and a clinically negative neck (T2N0). (*A*) The lesion covered the retromolar trigone, extended slightly onto the buccal mucosa, involved the lingual gingiva and the lateral margin of the tongue, and extended onto the soft palate to within 1.5 cm of the midline. Posteriorly, the lesion extended nearly to the tonsil. Treatment options included surgical resection followed by postoperative irradiation or irradiation alone. The patient was made aware that there was probably some decreased chance of cure by using radiation therapy as the initial treatment as opposed to combined treatment. He elected to accept the increased risk of recurrence to avoid the functional losses associated with surgical excision. (*B*) After 1800 cGy, marked tumoritis and mucositis were present. The patient was treated with parallel opposed fields weighted 2 : 1 left to right, ^{60}Co. The final dose was 7500 cGy over 8 weeks. (*C*) Appearance 2½ years after radiation therapy; no evidence of recurrence or necrosis. Patient was living, free of disease, at 3 years.

Figure 16-64. Squamous cell carcinoma of the left upper gingiva. There was no bone involvement. The resection included the periosteum. Note leukoplakia on the buccal mucosa.

tates a partial or total maxillectomy (Fig. 16-65). The defect is reconstructed with a prosthesis.

AMELOBLASTOMA. Ameloblastoma occurring in the mandible is best managed by mandibulectomy with adequate margins. Immediate reconstruction of the mandibular defect is usually done if little or no soft tissue is sacrificed; postoperative radiation therapy is rarely used as part of the initial therapy (Fig. 16-66).

The treatment of choice for ameloblastoma of the maxilla is partial maxillectomy with repair by a prosthesis. Curettage is unacceptable treatment in either the maxilla or mandible because it is accompanied by a high rate of recurrence.

Ameloblastoma responded readily to radiation therapy in two cases (Fig. 16-67). However, irradiation has generally been applied to patients after multiple operative failures or in cases of advanced disease. Therefore, the cure rate is unknown.

Figure 16-65. Squamous cell carcinoma of the right upper gingiva/hard palate with extension to the gingivobuccal sulcus. The lesion was fixed to the periosteum. Tomograms suggested early bone invasion. Treatment was partial maxillectomy.

Management of the Neck

PRIMARY LESION MANAGED BY SURGERY. Ipsilateral elective modified neck dissection is recommended for squamous cell carcinomas of the lower gum and retromolar trigone. The clinically involved neck is managed as outlined in Chapter 6.

PRIMARY LESION MANAGED BY IRRADIATION. Elective neck irradiation is recommended for squamous cell carcinomas of the lower gingiva and retromolar trigone. See Chapter 6 for the management of the clinically involved neck.

Surgical Treatment

RIM RESECTION (CORONAL RESECTION).* Early gingival and retromolar trigone lesions may be resected by an intraoral resection of the tumor that includes a cuff of normal periosteum or bone. Larger lesions of the lower gingiva and retromolar trigone, especially those fixed to the periosteum but with normal imaging studies, may be managed by rim resection, which allows preservation of the continuity of the mandible (Fig. 16-68).

SEGMENTAL MANDIBULECTOMY. For small lesions with minimal bone invasion, a short section of mandible is removed in continuity with the tumor (eg, removal of the mandible from the angle to the mental foramen). The mandible and tumor are resected from the mental foramen to the coronoid process; the head of the condyle usually remains intact (Fig. 16-69). If teeth are present in the remaining segment of the mandible, a K wire or cobalt–chromium alloy (Vitallium) mesh spacer with or without bone chips is used for rehabilitation. Otherwise, mandibular shift occurs after resection, which results in poor dental occlusion and difficulty in chewing (Fig. 16-70). In edentulous patients, no spacer is required, because the patient is rarely able to wear a lower denture. The cosmetic and functional loss after partial mandibulectomy is acceptable. K wires are not often used today because of their tendency to be extruded within a short period of time. The cobalt–chromium alloy mesh trays have a 60% to 75% success rate provided there is adequate soft tissue for coverage; postoperative irradiation has been used in some cases without obvious difficulties, but the success rate is probably reduced.

* The term *marginal resection* has sometimes been applied to the operation in which only a rim or coronal section of mandible is removed adjacent to the tumor but leaving the contour of the mandible intact. The term *marginal* suggests, however, that the operation gives very close borders to the neoplasm and, for this reason, is avoided.

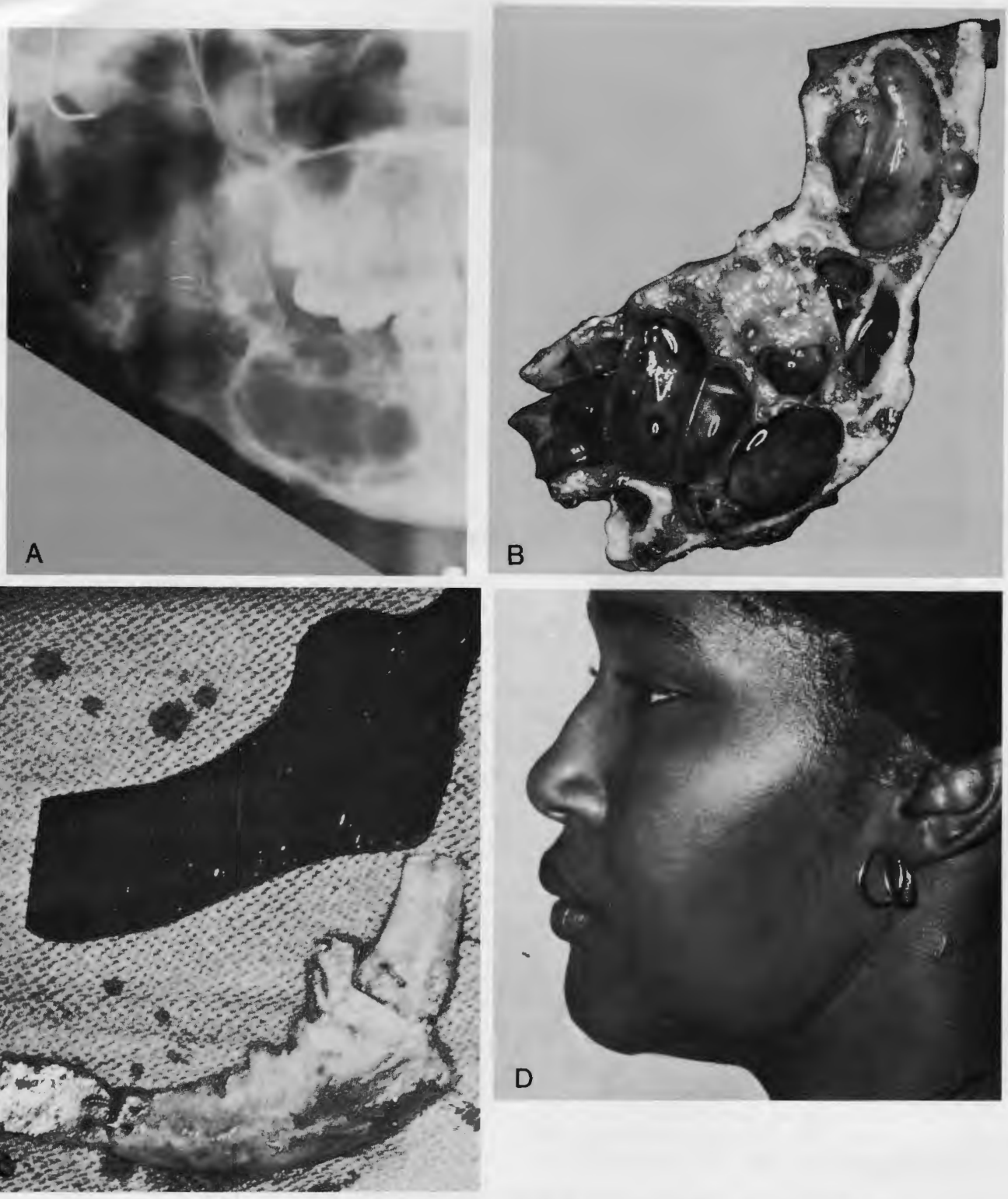


Figure 16-66. (*A*) Roentgenogram of ameloblastoma of the mandible. (*B*) Gross specimen. (*C*) Silhouette (*above*) of opposite normal mandible obtained from roentgenogram. Three pieces of bone from iliac crest fashioned to size and contour of contralateral mandible (*below*). (*D*) Postoperative appearance.

Figure 16-67. In 1962, an 18-year-old woman had a bone cyst and tooth removed. In 1965, she had a partial right mandibulectomy (diagnosis: ameloblastoma). In 1967, she had a right submandibular mass excised (diagnosis: ameloblastoma). In 1968, there was extensive recurrence in the right maxilla with extension to the zygoma, infratemporal fossa, right orbit, and right nostril and erosion into the oral cavity through the right upper posterior alveolar ridge (*A*). (*B*) Coronal tomograms revealed destruction of the right maxilla, zygoma, floor of the orbit, and ethmoid sinuses with possible extension to the clivus, sphenoid sinus, and cribriform plate. The patient was treated with 2-MV x-rays, receiving a minimum tumor dose of 5670 cGy by an anterior and right lateral wedge technique. (*C*) Complete regression of tumor was noted within 3 months. In 1970, the patient had facial reconstruction due to oral-antral fistula and bone necrosis. The chest roentgenogram showed lung nodules, and the diagnosis based on a biopsy specimen was ameloblastoma. In 1976, a small area of local recurrence was noted (diagnosis: ameloblastoma). A right lower lobectomy was done (diagnosis: ameloblastoma). Local recurrence in the right cheek was found in 1980, and wide local excision was done. In 1982, patient was living with local disease; the lung nodules were stable.

HEMIMANDIBULECTOMY. Extensive lesions may require removal of the mandible from symphysis to condyle on one side. Massive anterior lesions require removal of the mandible from angle to angle. This produces a major cosmetic and functional loss that is reconstructed with myocutaneous flaps, metal trays, and autogenous rib or iliac bone grafts.

PARTIAL MAXILLECTOMY. See Chapter 22.

Irradiation Technique

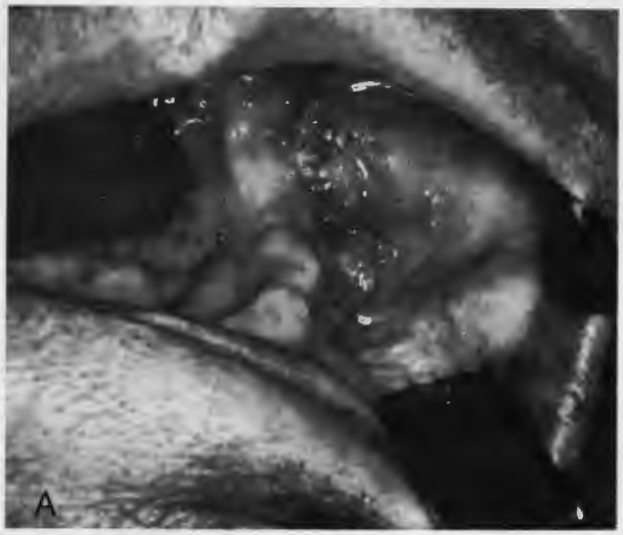
Small lesions of the lower gum and retromolar trigone may be treated by intraoral cone therapy for part of their therapy (Fig. 16-71). Well-lateralized lesions of the retromolar trigone may be treated by ipsilateral mixed-beam techniques or with angled-wedge techniques. A lead intraoral shield reduces contralateral irradiation with both techniques. Lesions of the anterior gingiva are treated by parallel opposed lateral portals or small angled wedge portals. The dose for retromolar trigone lesions is 6000 to 6500 cGy over 6 to 6½ weeks for T1 and T2 and 7000 cGy over 7 weeks for T3 lesions. The dose for gum lesions is similar. Intraoral cone therapy of 250 cGy per fraction for four to seven fractions may be substituted for part of the external-beam treatment.

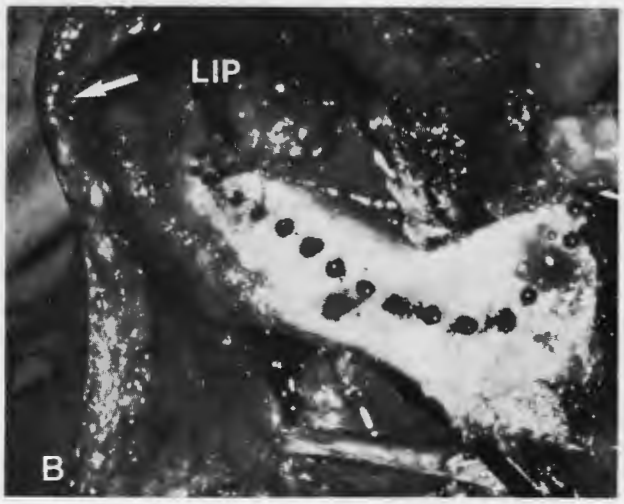
Management of Recurrence

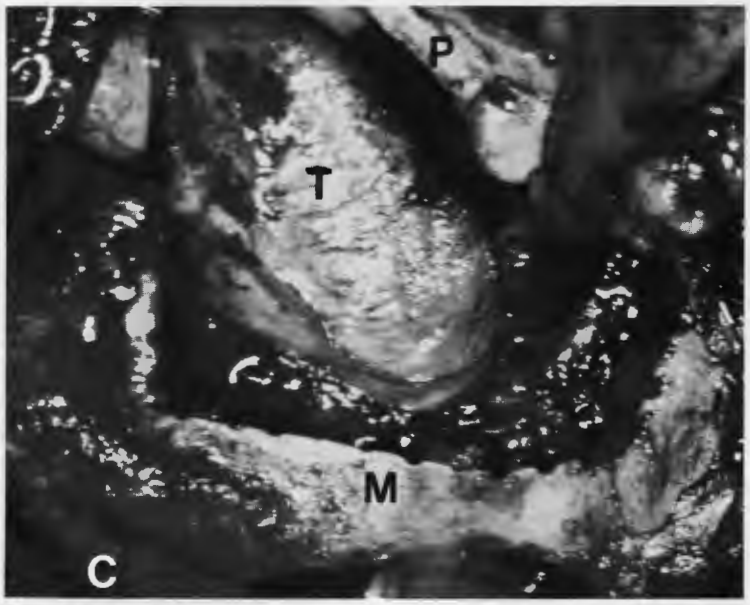
Radiation therapy failures may be managed by operation. Surgical failures may be managed by surgery, radiation therapy, or a combination of both.

(*text continues on page 398*)

Figure 16-68. (*A*) Squamous cell carcinoma of the left gingivobuccal sulcus (T2N0). (*B*) The lip was split and a cheek flap was elevated, exposing the body of the mandible. Drill holes were placed in the body of the mandible to facilitate a precision cut. (*C*) Rim resection was completed and specimen was removed; 1.0 to 1.5 cm of mandible remained intact. M, mandible; T, tongue; P, hard palate. (*D*) Intraoral defect after healing. (*E*) Contour of jaw is intact. This patient has an abnormal degree of hypertrophic scarring in the lip incision. For this reason, some surgeons prefer a visor-type flap.







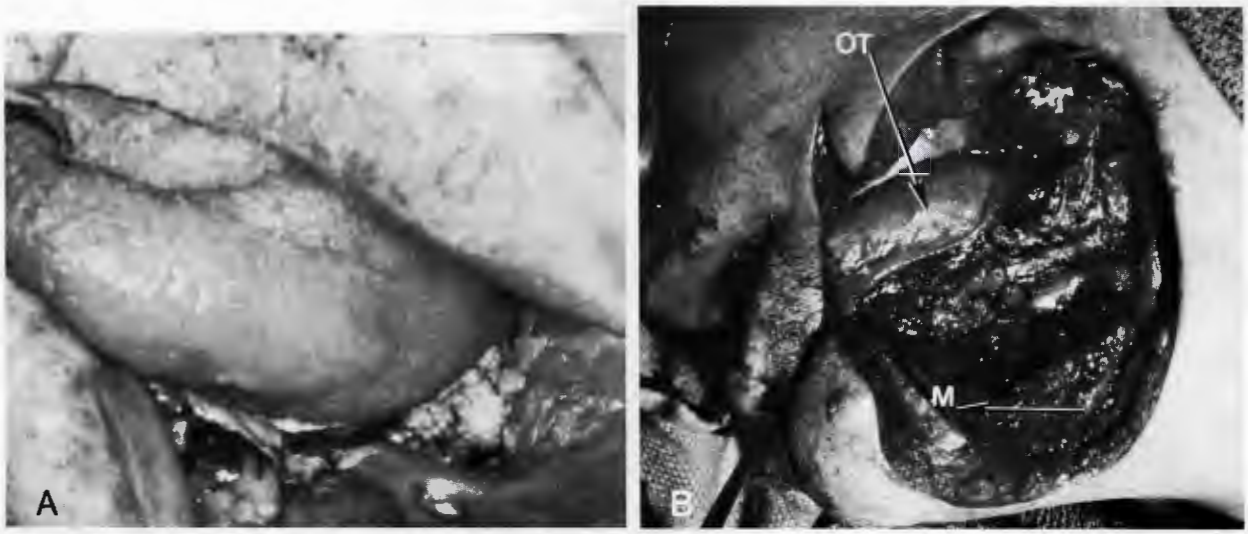


Figure 16-69. (*A*) Verrucous carcinoma of the alveolar ridge with excision to the floor of the mouth, buccal mucosa, and skin of the cheek. Roentgenograms showed mandible invasion. (*B*) A hemimandibulectomy plus resection of the floor of the mouth, buccal mucosa, and involved skin was done. OT, oral tongue; M, mandible (cut edge). (*C*) Rotation flaps were used to close the defect. The mandible was not reconstructed because of the large amount of soft tissue resected.

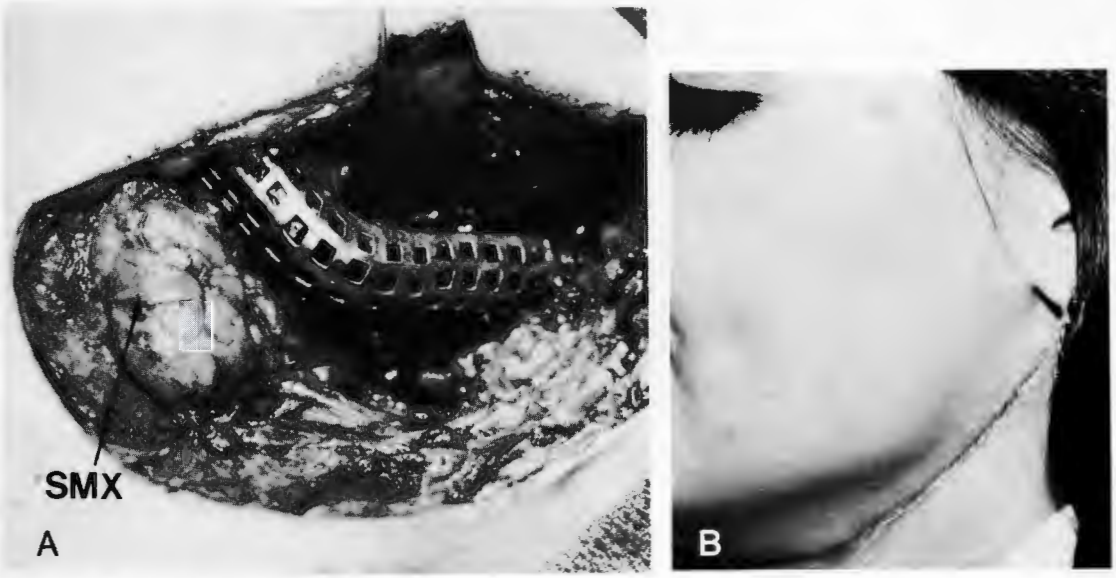


Figure 16-70. Hemangioendothelioma of the left mandible with soft tissue extension. (*A*) Replacement of left mandible with cobalt–chromium alloy (Vitallium) mesh spacer. SMX, submaxillary gland. (*B*) Postoperative appearance. Patient received postoperative irradiation, 6500 cGy. There was no evidence of disease at 10 years.

Figure 16-71. (*A*) Squamous cell carcinoma of the right retromolar trigone with extension to the anterior tonsillar pillar and soft palate (T2N0) in a 67-year-old woman. There was leukoplakia of the buccal mucosa and soft palate. Treatment plan: (1) intraoral cone, 3.5-cm diameter, 250 kV, Thoreus III, 300 cGy for each of five treatments for a total of 1500 cGy; (2) right face, 5000 cGy over 5 weeks, and right low neck, 4050 cGy over 3 weeks, ^{60}Co. (*B*) External-beam portal. (*C*) Simulator port film. Lead "lollipop," 4 cm thick, inserted in oral cavity to decrease irradiation to the opposite side. (*D*) Radiation mucositis confined to the right side. (*E*) There was no evidence of disease at 5 years. The patient reported 50% return of saliva. Note that the leukoplakia originally present on the buccal mucosa and soft palate disappeared.

Results of Treatment

Carcinoma

Fayos (Fayos JV, personal communication, June 7, 1974) reviewed 44 patients with squamous cell carcinoma involving bone and treated by radiation therapy; 29 patients had primary lesions of the lower gingiva. Local control by radiation therapy alone for lesions with early bone invasion (erosion defect) was approximately 50% (8 of 17) and for extensive invasion, about 25% (7 of 25; Fig. 16-72). Fayos'[22] report included 29 patients with squamous cell carcinoma of the lower alveolus.

Cady and Catlin[14] reviewed 606 patients with squamous cell carcinoma of the gingiva treated by surgery between 1942 and 1961 and reported an absolute 5-year survival rate of 43% (cause-specific, 53%) for patients with lower gum lesions and 40% (cause-specific, 47%) for those with upper gum lesions. The Memorial Sloan-Kettering series was updated in 1988. A total of 252 patients were eligible for 5-year analysis. Seventy had lesions of the retromolar trigone. Surgery was the treatment in 97%. The 5-year cause-specific survival was 54%. The 5-year actuarial survival was 77% for stage I, 70% for stage II, 42% for stage III, and 24% for stage IV. The results for upper and lower gum lesions were similar. Prior dental extraction, bone invasion, and involved surgical margins predicted a lower survival rate. Local recurrence occurred in 29%, and neck recurrence alone occurred in 9%. Twelve percent of patients with recurrences were salvaged by subsequent therapy.[74]

Byers and coworkers[11] reported a 5-year absolute survival rate of 43% for 61 patients with squamous cell carcinoma of the lower gum treated from 1970 to 1975. Fifty-one patients were managed by surgical resection. Intraoral resection including a rim of bone was selected for 28 early lesions. There was only one local failure. Eight patients subsequently developed neck node metastases; all were controlled. Segmental mandibulectomy and neck dissection were used for 23 patients with more advanced disease; there were no local failures. Three had recurrence in the neck, and all were salvaged. Six additional patients were given postoperative radiation therapy for close margins, perineural invasion, or extensive nodal metastasis; one patient had failure in the neck. The overall rate of control above the clavicles for operation with selected use of postoperative radiation therapy was 95%.

Shibuya and associates[69] reported the irradiation results for 120 cases of malignant lesions of the upper gum and hard palate, including 87 cases of squamous cell carcinoma. The 5-year survival rate for squamous cell carcinoma of the hard palate was approximately 45% and for the upper gingiva, approximately 45%. For patients with minimal bone invasion and a negative neck, the 5-year survival rate was 75%. A surprisingly high overall incidence of distant metastasis was observed of 49% for upper gum lesions and 50% for hard palate cases.

Ameloblastoma

Sehdev and associates[68] reported that curettage was followed by local recurrence in 90% of mandibular and all maxillary ameloblastomas. Subsequent resection controlled 80% of the mandibular tumors but only 40% of the maxillary tumors. The initial use of segmental mandibular resection controlled 78% (18 of 23), with subsequent resection controlling the treatment failures. The use of partial maxillectomy as the first treatment controlled 100% (7 of 7) of maxillary ameloblastomas as opposed to only 40% when partial maxillectomy was performed for recurrence. Hemimandibulectomy controlled 100% of curettage failures in one series.[64]

Follow-Up Policy

Ulceration with persistent recurrent pain may indicate either necrosis or cancer, and biopsy is required to establish the diagnosis. Ninety percent of recurrences appear within 3 years.

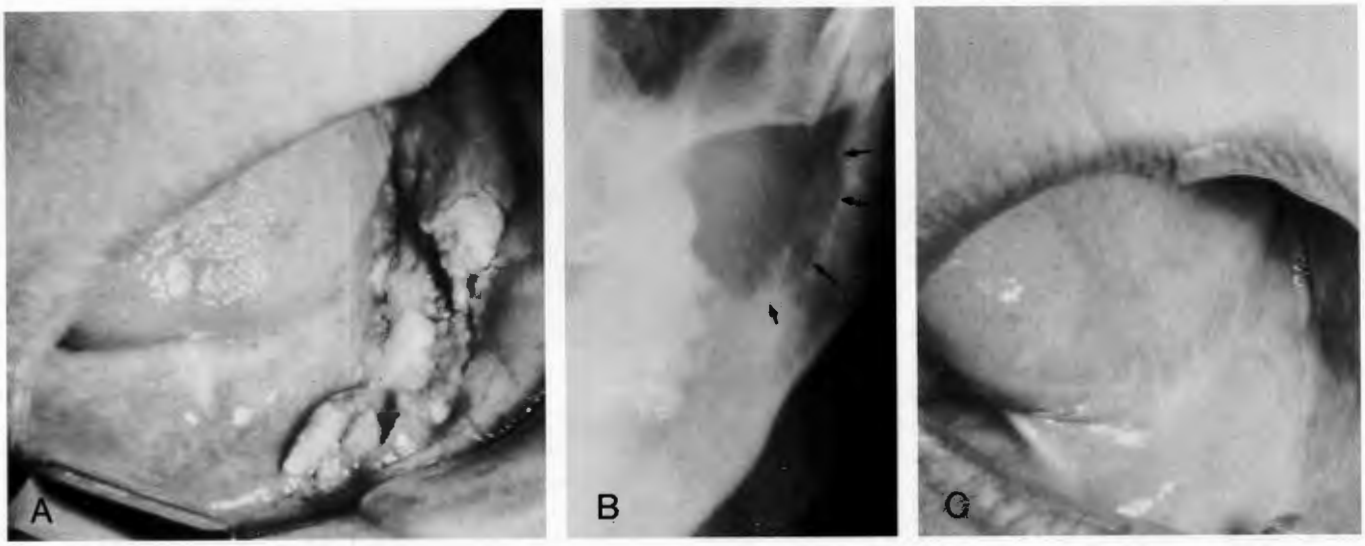


Figure 16-72. (*A*) Squamous cell carcinoma of the left lower gum (T4N0). Patient refused mandibulectomy. (*B*) Erosion (saucerization) of mandible (*arrows*). (*C*) Appearance 6 months after 6500 cGy over 7 weeks, ^{60}Co. Patient was free of disease at 6 years. There were no complications.

Complications of Treatment

Surgical complications include orocutaneous fistula, bone exposure with sequestration, and loss of graft or flap. The complications of radiation therapy include dental caries and soft tissue necrosis and bone exposure with subsequent osteoradionecrosis. The risk is greatest for patients with advanced lesions of the lower gum and retromolar trigone.

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17

OROPHARYNX

RODNEY R. MILLION, NICHOLAS J. CASSISI, AND ANTHONY A. MANCUSO

The oropharynx includes four areas: (1) the base of the tongue, (2) the tonsillar region (tonsillar fossa and tonsillar pillars), (3) the soft palate, and (4) that portion of the pharyngeal wall between the pharyngoepiglottic fold and the nasopharynx. The oropharyngeal walls are considered in Chapter 20.

ANATOMY

The base of the tongue is bounded anteriorly by the circumvallate papillae, laterally by the glossopharyngeal sulci, and posteriorly by the epiglottis. The vallecula is a 1-cm, smooth strip of mucosa that is the transition from the base of the tongue to the epiglottis; it is considered as part of the base of the tongue. The surface of the base of the tongue appears irregular and "bumpy" owing to scattered submucosal lymphoid follicles; the mucous membrane itself is actually smooth compared with the dorsum of the oral tongue. The surface of the base of the tongue is nearly parallel to the posterior pharyngeal wall. The musculature of the base of the tongue is continuous with that of the oral tongue and the floor of the mouth anteriorly. Figures 17-1 and 17-2 demonstrate anatomic relationships.[7]

The tonsillar area is a triangular region bounded anteriorly by the anterior tonsillar pillar (palatoglossal muscle), posteriorly by the posterior tonsillar pillar (palatopharyngeal muscle), and inferiorly by the glossotonsillar sulcus and pharyngoepiglottic fold. The palatine (faucial) tonsil lies within the triangle. The tonsillar region is bounded laterally by the pharyngeal constrictor muscle and its fascia, the mandible, and the lateral pharyngeal (parapharyngeal) space. The ascending pharyngeal artery and tonsillar and associated palatine branches of the maxillary artery are separated from the tonsil by the constrictor muscle. These lie within the lateral pharyngeal space. The internal carotid artery lies 2 to 3 cm laterally and posteriorly to the tonsil.

The tonsillar area is separated from the base of the tongue by the glossotonsillar sulcus. This narrow sulcus extends from the anterior tonsillar pillar to the pharyngoepiglottic fold. Just beneath the mucous membrane of the sulcus are the styloglossus muscle and the stylohyoid ligament.

The soft palate is a thin, mobile muscle complex that separates the nasopharynx from the oral cavity and oropharynx. The epithelium of the oral surface of the soft palate is squamous, and the epithelium of the nasopharyngeal surface is respiratory. The soft palate is contiguous laterally with the tonsillar pillars.

PATHOLOGY

Squamous cell carcinoma or one of its variants accounts for 95% of malignant lesions. Lymphoepithelioma occurs in the tonsil and base of the tongue. Verrucous carcinoma occurs rarely. Malignant lymphomas account for about 5% of tonsillar malignancies and 1% to 2% of malignancies of the base of the tongue. Minor salivary gland malignancies, plasmacytoma, and other rare tumors make up the remainder.

PATTERNS OF SPREAD

Base of the Tongue

Primary Lesion

Squamous cell carcinoma of the base of the tongue tends to early, silent, deep infiltration, and therefore the extent of tumors of the base of the tongue is usually underestimated by clinical examination. Tumors originating in the tongue base tend to remain there unless they begin in the peripheral margin. Tonsillar cancers tend to invade the base of the tongue, but base of the tongue cancers show little tendency to spread to the palatine tonsils. Vallecular lesions are often relatively exophytic

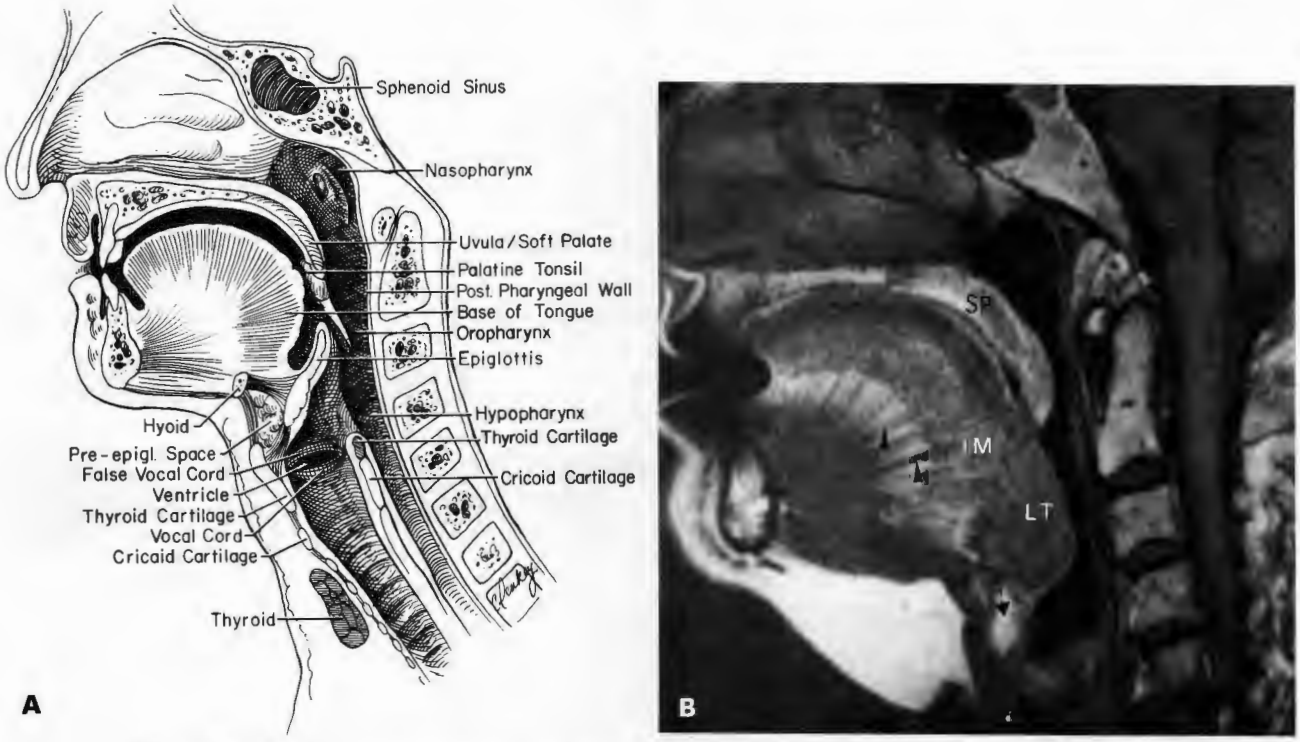


Figure 17-1. (*A*) Sagittal section of the upper aerodigestive tract. (*B*) Sagittal MRI. Note that the lymphoid tissue at the tongue base (LT) does not penetrate the intrinsic tongue muscles (IM); it is limited to the surface. Note how the genioglossus fibers fan out in the tongue (*arrowheads*) to finally interdigitate with the intrinsic tongue musculature. The tongue base is continuous with the preepiglottic space (*arrow*). Areas of high signal intensity within the soft palate (SP) are due, in part, to its fatty content. (*A*, redrawn from Sobotta drawings. In: Clemente CD, ed: Anatomy: a regional atlas of the human body, ed 3. Munich, Urban & Schwarzenberg, 1987)

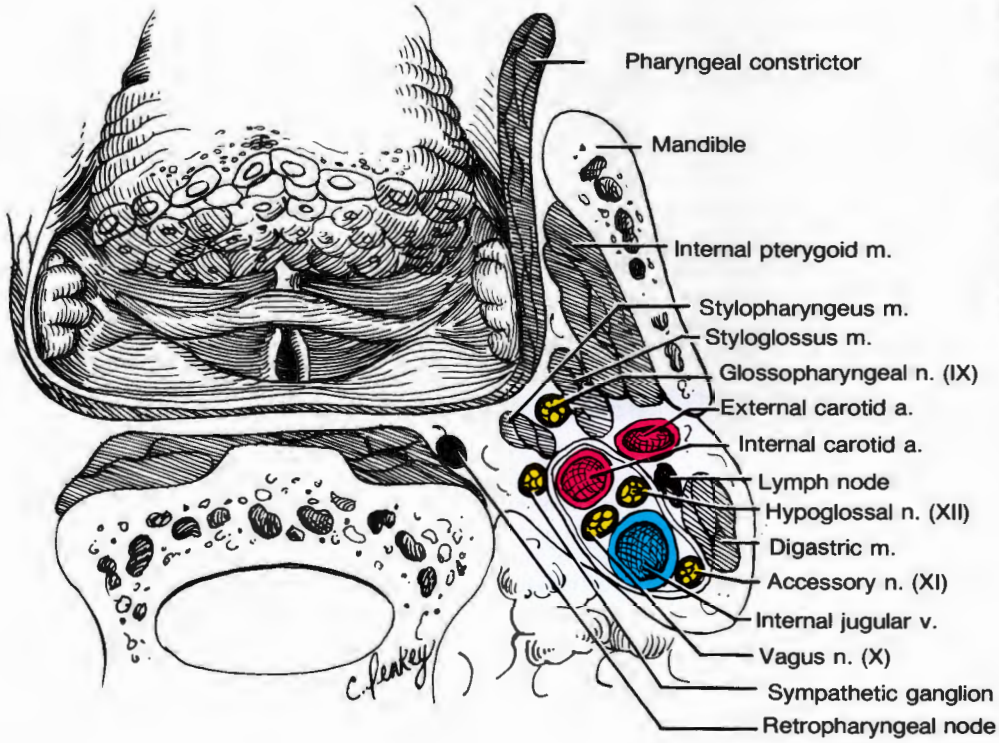


Figure 17-2. Section at the level of the mid oropharynx to show relationships in the parapharyngeal spaces. MRI anatomy is seen in Figures 16-12 and 16-13. (Million RR, Cassisi NJ, Clark JR. Cancer of the head and neck. In: DeVita VT Jr, Hellman S, Rosenberg SA, eds: Cancer: principles and practice of oncology, ed 3. Philadelphia, JB Lippincott, 1989:523)

and spread along the mucosa to the lingual surface of the epiglottis, laterally along the pharyngoepiglottic fold, and then to the lateral pharyngeal wall and anterior wall of the pyriform sinus. The vallecular cancers may penetrate through the thin mucous membrane of the vallecula; tumor spread may be contained for a while by the hyoepiglottic ligament, but this thin, often incomplete structure is eventually breached and cancer enters the preepiglottic space. Occasionally, cancers within the tongue base may spread into the preepiglottic space entirely beneath intact mucosa (see section on anatomy in Chap. 18). The best way to evaluate such spread is by computed tomography (CT) or magnetic resonance imaging (MRI).

Lesions that begin on the lateral base of the tongue may invade the glossotonsillar sulcus. Anterior spread may continue forward into the floor of the mouth deep within the sublingual space and not be visible or palpable. Direct lateral growth allows tumor to escape into the neck, since there is no effective muscular barrier at this point. The mylohyoid muscle is an effective barrier for oral tongue lesions, but the mylohyoid terminates near the angle of the mandible. The base of tongue mass may grow inferiorly and laterally and become palpable below the angle of the mandible because of direct spread into the soft tissues of the deep neck. This spread may be indistinguishable from an involved lymph node. Sometimes, both direct spread and lymph nodes are present. Once tumor spreads into the soft tissues of the neck, it can surround and invade the stylopharyngeus, styloglossus, and stylohyoid muscles and spread either superiorly or inferiorly along these muscle groups to their origins and insertions. Continued posterolateral growth can occasionally encase the carotid artery.

Lymphatic Spread

The distribution and staging of neck node metastases on admission prior to treatment for 185 previously untreated patients with squamous cell carcinoma of the base of the tongue are shown in Figure 17-3.[19] The first-echelon nodes are the subdigastric; the path of spread is then along the jugular chain to the midjugular and lower jugular nodes. The submandibular nodes may become involved if tumor extends anteriorly into the oral tongue or if massive upper neck disease is present. Submental spread is rare. The posterior cervical nodes are involved often enough to be included in treatment plans. Advanced lesions may involve the retropharyngeal lymph nodes.

About 75% of patients with cancer of the base of the tongue have clinically positive neck nodes on admission; 30% have bilateral nodes. By stage, the incidence of clinically involved lymph nodes is 70% for T1 to T2, 75% for T3, and 84% for T4 (see Table 6-3). The incidence of occult disease in clinically negative necks is reported at 22%,[26] but this figure is undoubtedly low, considering the selection of smaller lesions for operation and the use of preoperative irradiation. The actual risk for occult disease is estimated to be 30% to 50%. The distribution of involved lymph nodes in the clinically negative (N0) neck as shown by elective neck dissection for 10 patients with T3 or T4 lesions is given in Figure 17-4.[5]

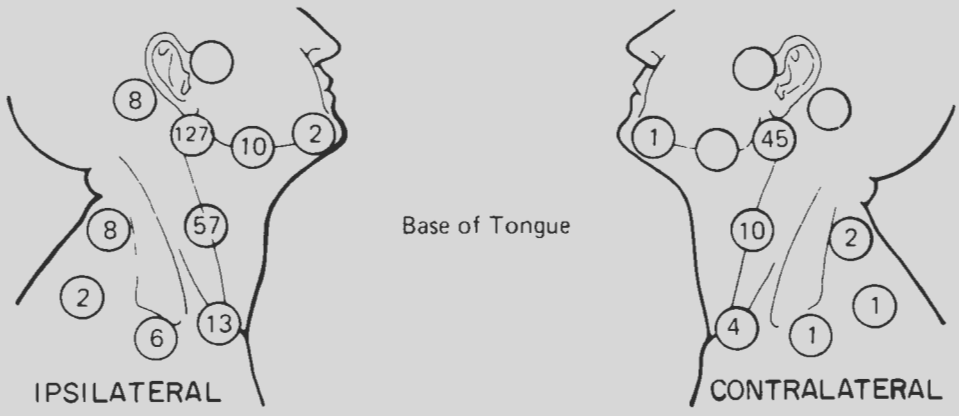
Tonsillar Area

The tonsillar area includes the anterior and posterior tonsillar pillars and the tonsillar fossa. Some authors group retromolar trigone lesions with the anterior tonsillar pillar lesions (because both areas are often involved simultaneously), but the retromolar trigone lesions are more appropriately considered as oral cavity lesions and grouped with the gingival (gum) lesions.

There are subtle differences in the spread patterns, clinical findings, treatment, and prognosis within the tonsillar area. When the lesions are early, the site of origin may be determined, but the more advanced lesions usually involve most if not all of the tonsillar area.

Anterior Tonsillar Pillar

Almost all malignant tumors arising on the anterior tonsillar pillar are squamous cell carcinomas. Asymptomatic mucosal lesions are common and may be red lesions, white lesions, or a mixture. Leukoplakia is frequently of the speckled variety. The borders of red lesions are often indistinct. The early discrete lesions tend to be flat with relatively little bulk or infiltration. As the lesions progress, they may develop a central ulcer



N_0	N_1	N_{2A}	N_{2B}	N_{3A}	N_{3B}	N_1–N_3 / Total
41	30	21	26	14	53	144 / 185 = 78%

Figure 17-3. Nodal distribution on admission at M. D. Anderson Hospital, 1948–1965, for carcinoma of the base of the tongue. (Lindberg RD. Distribution of cervical lymph node metastases from squamous cell carcinoma of the upper respiratory and digestive tracts. Cancer 1972;29:1449)

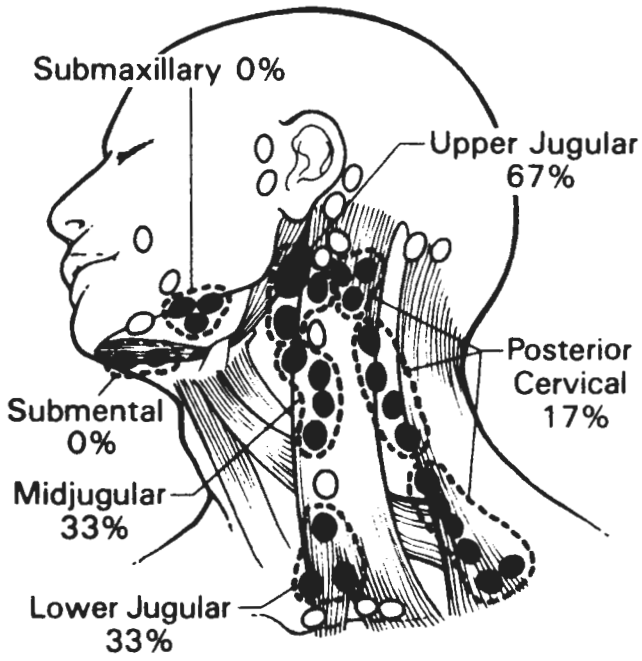


Figure 17-4. Carcinoma of the base of the tongue: Distribution of involved lymph nodes in the clinically negative neck as shown by elective neck dissection (10 patients with T3–T4 lesions). (Byers RM, Wolf PF, Ballantyne AJ. Rationale for elective modified neck dissection. Head Neck Surg 1988;10:164)

with a rolled margin and infiltrate the palatoglossal muscle. Superomedial spread occurs onto the soft palate, the most posterior hard palate, and the maxillary gingiva, but invasion of the maxilla is uncommon. Anterolateral spread to the retromolar trigone is common, with subsequent spread to the posterior gingivobuccal sulcus and buccal mucosa. Once the tumor gains access to the buccal mucosa, there is a risk for anterior subclinical extension into the buccal space and low infratemporal fossa, as exemplified by anterior marginal failure in patients treated by irradiation or operation.

Invasion of the tongue is frequent; careful palpation is necessary to detect the early submucosal nodule at the junction of the anterior tonsillar pillar and tongue.

As these lesions advance they adhere to the mandible and eventually invade the bone. Extension toward the base of the skull and nasopharynx is a late phenomenon, usually associated with infiltration of the pterygoid muscles and possible erosion of the medial pterygoid plate; such lesions produce trismus and marked temporal pain.

Tonsillar Fossa

Tonsillar fossa lesions arise either from the remnants of the palatine tonsil or from the mucous membrane within the triangle. There are some differences in development and spread patterns for squamous cell carcinomas of the tonsillar fossa compared with anterior tonsillar pillar lesions. Leukoplakia rarely occurs within the fossa, and asymptomatic red mucosal lesions are infrequently seen. The tonsil is a common site for entirely submucosal lesions that may present as a cervical metastasis. The initial mucosal lesions tend to be exophytic. Central ulceration plus an infiltrative component develops as the lesion expands. Extension to the posterior tonsillar pillar and the oropharyngeal wall is common. Invasion into the glossotonsillar sulcus and the base of the tongue occurs in about 25% of cases. As the lesions advance they penetrate the pharyngeal constrictor to the parapharyngeal space, and advanced lesions may even gain access to the base of the skull superiorly. Cranial nerve involvement, however, is uncommon. Advanced lesions invade the mandible, nasopharynx, and base of the tongue and may extend below the pharyngoepiglottic fold into the pyriform sinus.

Posterior Tonsillar Pillar

Discrete lesions arising from the posterior tonsillar pillar are uncommon and for some unknown reason have an evil reputation. The only two lesions we have seen were 1.0- to 1.5-cm, discrete lesions with a raised border and central ulceration, and both were cured. There are two major differences in their potential spread patterns. First, they may spread inferiorly along the palatopharyngeal muscle to its three points of insertion: (1) the middle pharyngeal constrictor, (2) the pharyngoepiglottic fold, and (3) the posterior border of the thyroid cartilage. Second, the junctional, spinal accessory, and probably the retropharyngeal lymph nodes are more likely to be involved.

Lymphatic Spread

The distribution and N staging on admission prior to treatment for previously untreated patients with retromolar trigone/anterior tonsillar pillar and tonsillar fossa squamous cell carcinomas are shown in Figure 17-5.[19]

Retromolar trigone/anterior tonsillar pillar lesions have a lower risk of clinically positive lymph nodes (45%) compared with tonsillar fossa (76%). The distribution for the retromolar trigone/anterior tonsillar pillar on the ipsilateral side is to the submandibular and internal jugular chain. The risk of occult disease in the clinically negative neck (N0) is 10% to 15%.[40] The incidence of positive nodes according to stage is about 11% for T1, 38% for T2, 54% for T3, and 68% for T4 lesions (see Table 6-3).

Tonsillar fossa lesions have a high risk of clinically positive lymph nodes (76%). The lymph node distribution for tonsillar fossa lesions on the ipsilateral side is mainly to the jugular chain lymph nodes. The spinal accessory and the more posterior submandibular lymph nodes are at risk. The incidence of positive lymph nodes is about 70% for T1 to T3 lesions and 90% for T4 lesions (see Table 6-3). Contralateral spread occurs in only 11% of patients and is mainly to the internal jugular vein lymph nodes, but there is a small risk for spinal accessory and submandibular involvement. The risk of contralateral spread is related to invasion of the tongue and to spread near or across the midline of the soft palate. Large lymph nodes in the ipsilateral neck may predict contralateral spread, but the risk of this occurrence is unknown. The incidence of subclinical disease after low-dose preoperative irradiation was 22%;[36] the actual risk is probably closer to 50% to 60%. Retropharyngeal lymph nodes are at risk in advanced lesions.

Discrete lesions of the posterior tonsillar pillar are uncommon, but they should have a pattern of lymph node distribution similar to the tonsillar fossa and the nasopharynx with a definite risk for retropharyngeal and spinal accessory lymph node involvement.

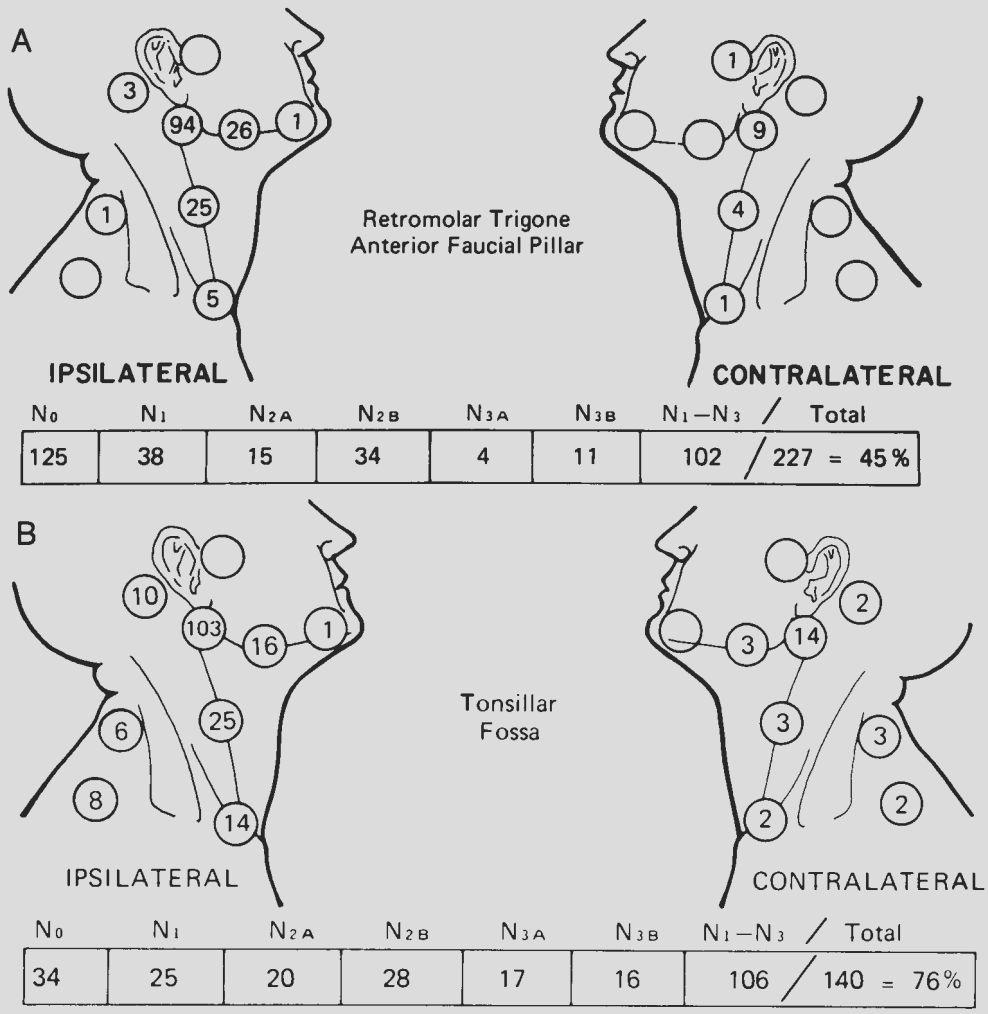


Figure 17-5. Nodal distribution on admission at M. D. Anderson Hospital, 1948–1965. (*A*) Carcinoma of the retromolar trigone and anterior tonsillar pillar. (*B*) Carcinoma of the tonsillar fossa. (Lindberg RD. Distribution of cervical lymph node metastases from squamous cell carcinoma of the upper respiratory and digestive tracts. Cancer 1972;29:1448)

Advanced lesions of the tonsillar fossa usually involve all three tonsillar areas, and the distribution of lymph node metastases assumes characteristics of the sites involved.

Soft Palate

Primary Lesion

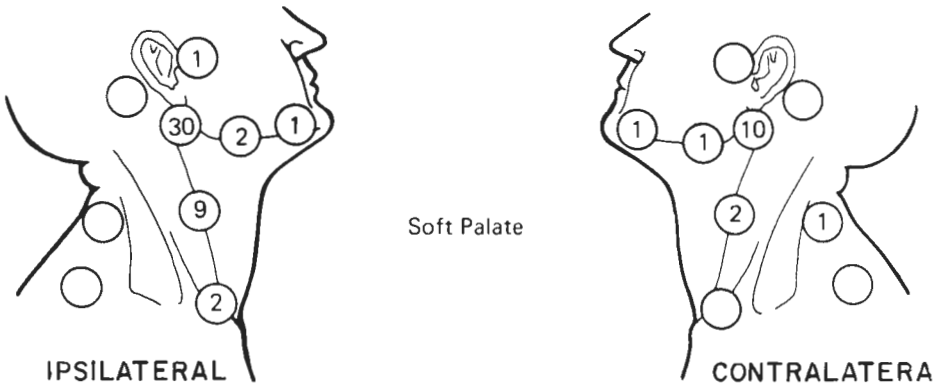
Nearly all soft palate squamous cell carcinomas occur on the oral side of the palate. The nasopharyngeal side seems nearly immune to tumor production, but primary lesions of the nasopharyngeal side of the soft palate have been seen in two instances in 30 years. Even large tumors of the nasopharynx seldom invade the soft palate.

The earliest carcinomas are red lesions with ill-defined borders similar to early lesions of the anterior tonsillar pillar. White lesions are common on the soft palate and may be leukoplakia, carcinoma in situ, or early invasive carcinoma. Multiple sites of involvement with normal-appearing intervening mucosa are common. This finding is dramatically demonstrated during the first week of radiation therapy when the abnormal epithelium at the tumor sites "lights up" (tumoritis).

The majority of soft palate carcinomas are diagnosed while still confined to the soft palate and adjacent pillars. The diameter of the lesions may qualify as T2 (2 to 4 cm) or T3 (greater than 4 cm), but the lesions may be rather thin with a relatively small tumor volume compared with T2 or T3 lesions of the base of the tongue or tonsillar fossa. Spread from the soft palate occurs first to the tonsillar pillars and hard palate. Involvement of the lateral walls of the nasopharynx and tonsillar fossa is common in advanced lesions. Advanced lesions may cause perforation or ulcerative destruction of the free margin of the soft palate. Lateral spread may eventually penetrate the superior constrictor muscle with subsequent invasion of the medial pterygoid muscle and compression or invasion of cranial nerves in the parapharyngeal space. Invasion of bone is uncommon. There is an especially high risk for second head and neck malignancies, and careful examination of all head and neck mucosal sites, the esophagus, and the lungs must be performed.

Lymphatic Spread

The distribution of neck nodes and N staging for previously untreated patients with squamous cell carcinoma of the soft palate is shown in Figure 17-6.[19] The lymphatic capillaries are particularly dense over the uvula.[37]



N_0	N_1	N_{2A}	N_{2B}	N_{3A}	N_{3B}	N_1–N_3 / Total
45	12	2	4	4	13	35 / 80 = 44%

Figure 17-6. Nodal distribution on admission at M. D. Anderson Hospital, 1948–1965, for carcinoma of the soft palate. (Lindberg RD. Distribution of cervical lymph node metastases from squamous cell carcinoma of the upper respiratory and digestive tracts. Cancer 1972;29: 1448)

The spread pattern is first to the subdigastric nodes and then along the jugular chain. The submandibular and spinal accessory lymph nodes are uncommonly involved. Extension to the anterior tonsillar pillar and retromolar trigone increases the risk of submandibular involvement. Retropharyngeal lymph node involvement occurs in advanced cases. Extension to the tonsillar fossa and posterior tonsillar pillar increases the risk of spinal accessory lymph node involvement.

About 44% have clinically positive lymph nodes on admission; 16% have bilateral nodes. The incidence of occult disease is not well established, since the first-echelon nodes are usually irradiated in all but the earliest lesions. Lindberg and coworkers noted about a 20% incidence of subclinical disease following either no or partial neck irradiation and with the primary lesion controlled.[20] The incidence of clinically positive nodes increases with T stage: 8% positive for T1, 36% for T2, and about 66% for T3 and T4 (see Table 6-3).

CLINICAL PICTURE

Base of the Tongue

Presenting Symptoms

Asymptomatic lesions are rarely diagnosed, since the base of the tongue is visualized only by indirect mirror examination. Many of the early lesions are relatively silent, and a subdigastric neck mass, which is often large, is frequently the first sign. The patient may insist that a 5-cm or larger neck mass "came up overnight." In a sense the patient is correct, since small clinically positive lymph nodes, 1 to 4 cm in diameter, are almost always asymptomatic. Sudden enlargement may occur due to necrosis or internal bleeding with rapid increase in size and mild tenderness.

The earliest symptom related to the tongue lesion is often a mild or vague sore throat. The patient may sense a lump in the back of the tongue, and some patients can feel it by digital palpation; the patient is not amused by the physician who fails to see the lesion with a tongue depressor and fails to palpate the base of the tongue. Difficulty in swallowing, a nasal quality to the voice ("hot potato voice"), and deep-seated ear pain occur as the lesion enlarges (see Fig. 16-17).

Far-advanced lesions fix the tongue. Deep ulceration and necrosis result in foul breath. Unilateral paralysis and atrophy of the tongue associated with hypoglossal nerve invasion is rare.

Physical Examination

Indirect mirror examination, digital palpation, and a high level of suspicion are needed for diagnosis. Early lesions are often submucosal and relatively soft; and since the surface of the base of the tongue is irregular, diagnosis is often a challenge. The rigid and flexible fiberoptic telescopes permit examination in some patients not easily visualized by indirect mirror examination. Examination may show only a slight bulge in the tongue. A small lesion (less than 1 cm) originating in the glossotonsillar sulcus area may ulcerate and produce symptoms early; it may be overlooked unless the area is examined by separating the tongue from the lateral pharyngeal wall and inspecting the sulcus. Palpation through the lateral floor of the mouth is the best method to detect anterior extension. Inferior penetration through the vallecula produces a fullness in the soft tissues around the hyoid bone. Fixation of the tongue causes incomplete protrusion or protrusion toward the side that is fixed. There is a tendency to underestimate the size of lesions of the base of the tongue.

Lymphomas are usually large submucosal masses and can be suspected by their appearance. Minor salivary gland tumors are also usually submucosal in their early phase but more discrete and firm than lymphomas.

Tonsillar Area

Anterior Tonsillar Pillar

Asymptomatic lesions are frequently found on routine examination by both dentists and physicians. Early symptoms include sore throat and ear pain, usually aggravated by swallowing. If the lesion involves the hard palate or posterior upper gum, dentures may fit improperly or cause irritation. Advanced lesions invade the pterygoid or buccinator muscles and produce trismus, dysphagia, and pain referred to the temple area. Invasion of the tongue will eventually limit tongue mobility and, when accompanied by ulceration at the junction of

the anterior tonsillar pillar and oral tongue, causes a great deal of pain.

Tonsillar Fossa

Signs and symptoms are similar to those for anterior tonsillar pillar lesions except that the lesions tend to be larger before symptoms develop. Ipsilateral sore throat and ear pain are the hallmark of these lesions. Detection by visual examination with a tongue depressor is sufficient for most lesions of the tonsillar fossa; however, a few cancers arise near the glossotonsillar sulcus or lower pole of the tonsil and are only visible by indirect examination. A few patients will present with a mass in the neck, and the primary site is only discovered after biopsy of a slightly abnormal tonsil or by tonsillectomy. Lymphomas of the tonsil tend to be large submucosal masses but may ulcerate and appear similar to carcinomas.

Soft Palate

The earliest symptom is usually mild sore throat, which is often aggravated by food or drink. The sore throat is not well localized; discomfort may improve temporarily if antibiotics are given. Advanced lesions interfere with swallowing and may cause a voice change. Regurgitation of food and liquid into the nasopharynx and nose occurs with destruction, perforation, or fixation of the soft palate. Lateral and superior spread to the nasopharynx and parapharyngeal space is associated with trismus, otitis media, temporal headache, and rarely cranial nerve involvement. Early lesions appear as red, white, or mixed changes in the mucosa; the mucosa may appear roughened and the tumor margins ill defined. Multiple foci on the soft palate and anterior tonsillar pillars are common. Moderately advanced lesions have rolled edges with central ulceration, or they may be mainly exophytic, particularly around the uvula. The nasopharynx should be inspected and palpated for extension along the lateral wall; extension along the nasopharyngeal surface of the soft palate is uncommon until the late stages. Extension to the posterior nasal cavity is seen only in advanced lesions that erode the posterior hard palate.

METHODS OF DIAGNOSIS AND STAGING

Biopsy Technique

Most lesions of the oropharynx can be biopsied by incisional or punch forceps biopsy using a local anesthetic in the outpatient setting. Lesions of the base of the tongue may require a general anesthetic. Frozen section control is helpful in lesions of the base of the tongue, since it is sometimes difficult to obtain representative tissue. Special handling of tissue is required if lymphoma is suspected (see Chap. 34).

Staging Procedures

Early lesions are staged by physical examination; direct laryngoscopy with the patient under general anesthesia may be required for base of the tongue and vallecular lesions.

Imaging

The main imaging tools of the oropharynx are CT and MRI. CT is the preferred initial study because it is better for the lymph nodes and bone detail, is less expensive, and provides more consistently high-quality studies. MRI is used adjunctively.

Technique of Examination

Basic CT and MRI techniques were reviewed in Chapter 4. Evaluation of the oropharynx should include sections from the nasopharynx to the lower neck. Axial sections usually suffice; however, coronal sections may occasionally be useful when lesions approach the skull base. Sagittal MRI is rarely necessary, except for a question of early preepiglottic space invasion by tongue base cancers.

Patients should be immobilized. On CT, breathing should be suspended for each section acquisition. With current techniques, the patients must be left to breathe quietly during the MRI examination. Axial sections made through the nasopharyngeal portion of the examination should be parallel to the infraorbital meatal line or the hard palate. CT sections should be angled to avoid artifacts from dental hardware, which may interfere with image quality at the junction of the oropharynx and nasopharynx. Sections from the middle of the oral cavity to the hyoid bone are best made parallel to the body of the mandible. The importance of proper angulation of sections through the oropharynx cannot be overstated. When sections are angled parallel to the body of the mandible, the anatomic relationships at the tongue base to the floor of the mouth and deeper structures of the neck make anatomic sense. If sections are far out of this plane, it may lead to a confusing display of the pathology relative to surgical as well as radiotherapeutic landmarks. Contiguous 3- to 4-mm sections should be used through the primary site and neck. It is important to keep the field of view as small as possible so that the pictures are magnified and spatial resolution is optimized.

CT and MRI studies of this region require injection of intravenous contrast media. The method and value of contrast studies are discussed in Chapter 4.

MRI examination requires the use of specialized receiver coils capable of covering the area from the craniocervical junction to the thoracic inlet. Standard T1- and T2-weighted images are the pulse sequences of choice for MRI examinations. In the near future, fat suppression techniques, and fast imaging techniques used in combination with fat suppression and contrast enhancement, may become standard.

Evaluation of the oropharynx must include a complete CT study of the cervical and retropharyngeal nodes.

Imaging of the Normal Anatomy

The normal CT and MRI anatomy of the oropharynx in axial sections is shown in Chapter 16.

Indications for Study

CT and MRI are excellent at showing the deep anatomy surrounding the pharynx. The deep tissue planes are generally symmetric, and obliteration of the deep fat spaces such as the parapharyngeal space or invasion of

deep musculature is a reliable sign of invasion. Such spread is frequently not expressed as signs and symptoms, nor detected by physical examination. This is especially true in the nasopharynx and upper oropharynx (deep to the faucial tonsils). Lower in the oropharynx, the pharyngeal wall becomes tightly surrounded by musculature and the intervening fat planes are less visible, making diagnosis of infiltration more difficult.

The tendency for the deeper tissue planes within the upper oropharynx to be symmetric must be contrasted to the marked variation in contours and symmetry of the superficial airway contours. Lymphoid tissue is present throughout the oropharynx and is responsible for most of the variation seen in the surface contours on CT and MRI. Unschooled interpreters of CT and MRI may frequently misinterpret various bumps and bulges on the mucosal surfaces for tumors. Bumps and bulges bordering the airway should either be ignored or be used as prompts to look for adjacent deep infiltration as a sign of pathology. These surfaces are best evaluated on physical examination and not by CT or MRI. There are no findings that can distinguish lymphoid tissue and other benign mucosal lesions from cancer other than infiltration of the deeper structures including the pharyngeal musculature, parapharyngeal space, muscles of the tongue, and other deep muscles such as the pterygoid group and those originating from the styloid process.

Any tumor that is suspicious for deep infiltration should be studied primarily with CT. Supplemental MRI study is directed by CT findings to a localized area of interest where its strengths related to soft tissue contrast resolution and multiplanar images may be exploited. A significant proportion of MRI studies of this area will be of low quality because of motion artifacts until rapid MRI techniques are perfected. It is estimated that MRI will be used as a complementary examination in 10% to 20% of patients, mainly to determine the extent of tumor within the tongue or to confirm evidence of deep spread of tumor to the styloid musculature or along the structures in and around the carotid sheath (poststyloid parapharyngeal space). MRI is, in general, preferred for the evaluation of the parapharyngeal space.

Specific indications for CT and MRI in the oropharyngeal region include the evaluation of the deep extent of primary tumors at all subsites, especially in regard to the following spread patterns:

- Submucosal spread within the visceral compartment (Fig. 17-7)
- Spread to and within the prestyloid parapharyngeal space (see Fig. 17-7)
- Spread to the styloid musculature and poststyloid parapharyngeal space, carotid sheath structures, and related cranial nerves (Fig. 17-8)
- Spread to the infratemporal fossa, the masticator space, and neurovascular bundles within these spaces (Fig. 17-9)
- Bone involvement, which is a rare occurrence for primary lesions of the oropharynx

For carcinomas of the glossotonsillar sulcus and base of the tongue (Figs. 17-10 and 17-11), the physical examination is limited in evaluating the deep extent of the tumor. CT and MRI produce excellent maps of glossotonsillar sulcus and tongue base cancers and their relationship to the floor of the mouth and oral tongue. Spread within the tongue base and glossotonsillar sulcus may be directed anteriorly to the floor of the mouth along the mylohyoid muscle and within the sublingual space. This may occur in the absence of palpable disease in the floor of the mouth. The relationship of tumor margins to both lingual neurovascular bundles can be anticipated on imaging with far greater precision than on physical examination. Occasionally, retrograde spread of tumor out of the tongue along the lingual neurovascular bundles to the external carotid artery will be visible. Tumors in the region may also grow onto the styloid musculature as described earlier. Inferior growth along the mylohyoid and hyoglossus muscles may bring the tumor to the insertion of these muscles on the hyoid bone, and there may be direct extension into the soft tissues of the suprahyoid and infrahyoid neck at that point. Occult spread from the tongue base to the preepiglottic space may also be visualized.

For the use of imaging studies for evaluation of retropharyngeal and cervical nodes, see Chapter 6.

CT and MRI are indicated for the evaluation of submucosal oropharyngeal masses of uncertain etiology. Patients will occasionally present with a mass covered by intact mucosa in the oropharyngeal region. These submucosal masses often turn out to be benign tumors in the parapharyngeal space, such as paragangliomas or schwannomas from the poststyloid parapharyngeal space or benign mixed tumors arising either in the deep portion of the parotid gland or in the prestyloid pharyngeal space. A submucosal, pulsatile or nonpulsatile mass in the oropharynx should be studied with MRI or, at minimum, CT before biopsy. Imaging before biopsy could avoid injury to the carotid artery or bleeding, which is difficult to control. Imaging, especially with MRI, in these lesions will frequently redirect the diagnostic and therapeutic plan. This is discussed more fully in Chapter 23. Any patient who is thought to have recurrent tumor should immediately have a baseline imaging study (usually CT).

Staging

All oropharyngeal sites are included in one T-stage system:[2]

Tis	Carcinoma in situ
T1	Tumor 2 cm or less in greatest diameter
T2	Tumor more than 2 cm but not more than 4 cm in greatest diameter
T3	Tumor more than 4 cm in greatest diameter
T4	Tumor invades adjacent structures (eg, through cortical bone, soft tissues of neck, deep (extrinsic) muscle of tongue)

There is a tendency to overestimate the diameter of lesions of the palate and tonsil; insertion of a measuring device will help judge the maximum diameter. The difference between T3 and T4 is not so easily determined. It is difficult to distinguish between direct invasion of soft tissues of the neck and a deep lymph node mass. Tumors of the tonsillar area or base of the tongue that penetrate the glossopharyngeal sulcus can frequently be palpated as a deep mass just under the angle of the jaw and qualify as stage T4 if the primary lesion is larger than 4 cm in diameter; bimanual palpation and CT scan help outline the continuity of the mass. Fixation of the tongue indicates invasion of the root or deep musculature of the tongue. If cancer of the base of the tongue can be palpated easily through the lateral floor of mouth or in the

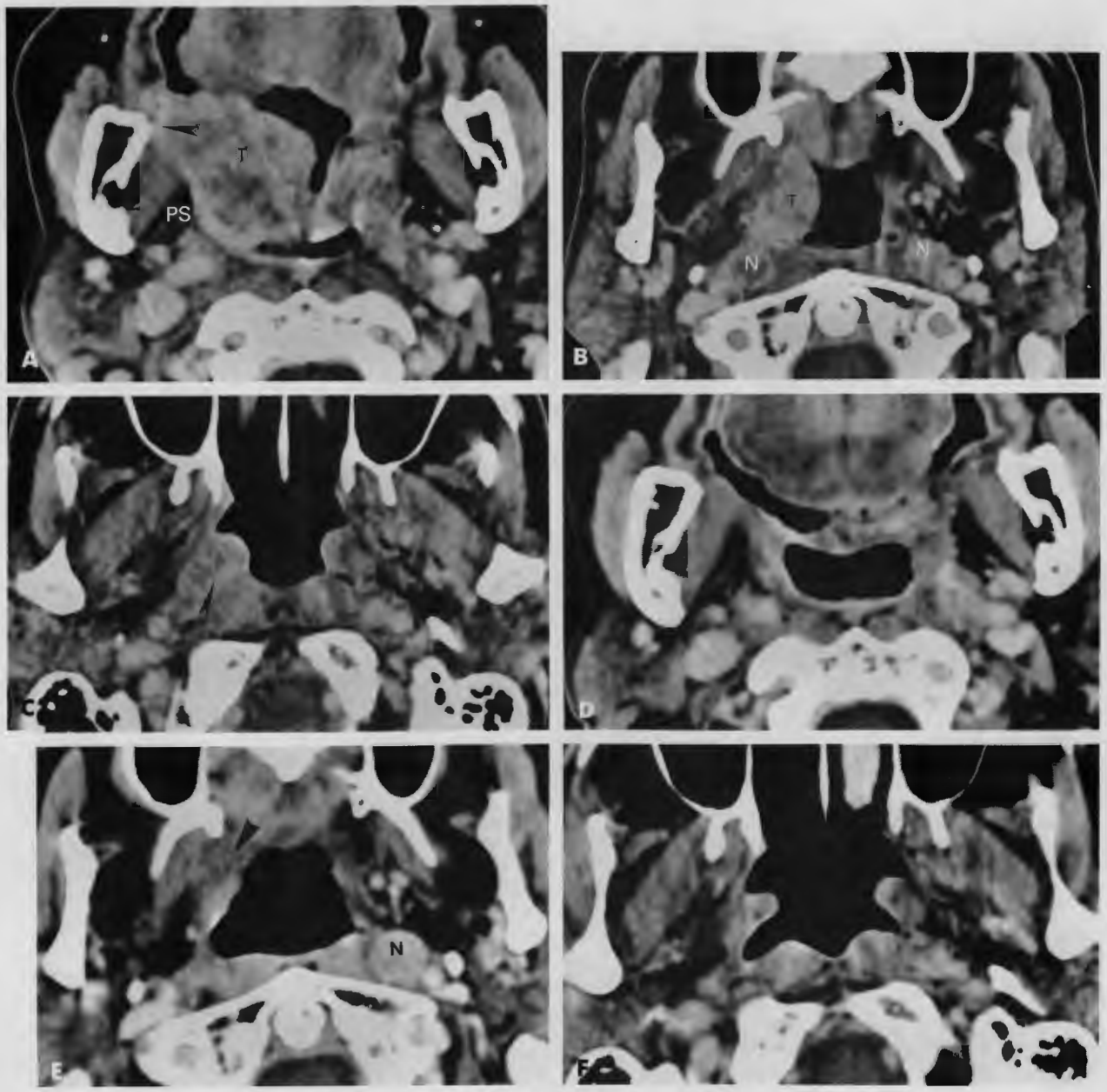


Figure 17-7. This middle-aged woman had a tonsillar cancer that involved the soft palate. There was no definite evidence of mucosal abnormality in the nasopharynx, although a submucosal bulge could be seen low in the nasopharynx. (*A*) The very bulky tumor (T) has an exophytic component bulging into the airway. Deep infiltration of the tumor extends to the pterygomandibular raphe (*arrowhead*) and obliterates the anterior portion of the pharyngeal space (PS); compare to the opposite parapharyngeal space. (*B*) Section through the low nasopharynx shows continued cephalad spread of tumor (T) to involve the lateral wall of the nasopharynx. Bilateral retropharyngeal nodes (N), definitely positive by CT criteria, are also present. (*C*) Tumor is still seen obliterating the deep tissue planes (*arrowhead*) around the fossa of Rosenmüller and torus tubarius at the mid-pharyngeal level. (*D* through *F*) Sections made at levels identical to those seen in *A* through *C*. There is virtually complete response of the primary tumor to radiotherapy, leaving only minimal residual tissue thickening (*arrowhead*) consistent with some postirradiation scarring. However, the left retropharyngeal node (N) did not respond completely to therapy and, in fact, appears slightly larger, suggesting persistent tumor.

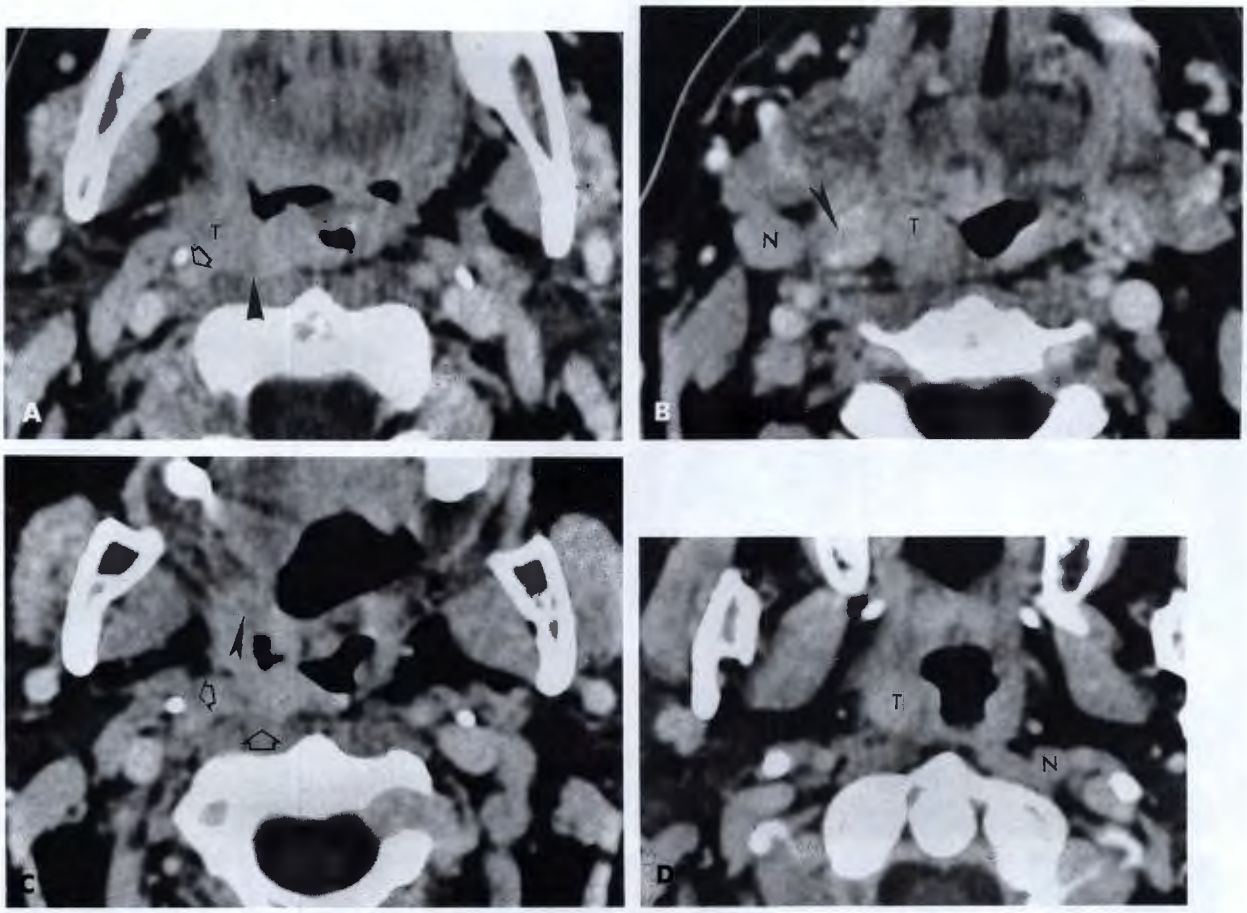


Figure 17-8. A middle-aged woman had a carcinoma of the posterior tonsillar pillar. (*A*) Section through the mid-tonsillar fossa shows an infiltrating tumor (T) involving the entire tonsillar fossa but centered near the junction of the posterior tonsillar pillar and pharyngeal wall. Note the obliteration of the fat plane in the retropharyngeal space (*arrowhead*), as well as direct spread to the poststyloid parapharyngeal space (*open arrow*). (*B*) Section through the oropharynx about midway between the circumvallate papillae and the valleculae. Infiltrating tumor (T) is present. This lower aspect of the tumor correlated with a submucosal bulge in the region, although no obvious mucosal disease was present. Nodal metastasis is also present (N). Also note obliteration of tissue planes in the parapharyngeal space, especially around the branches of the external carotid artery (*arrowhead*); compare with normal side. (*C*) At the junction of the tonsillar fossa and soft palate, the tumor also involves the anterotonsillar pillar (*arrowhead*). There is obliteration of the tissue planes in the retropharyngeal space and the poststyloid parapharyngeal space (*open arrows*). This appears to be due to direct extension of the tumor rather than a retropharyngeal node. (*D*) In the low nasopharynx there is continuation of tumor along the posterolateral pharyngeal wall (T). Much of this disease was also submucosal. Note the positive contralateral retropharyngeal node (N).

submentum, then invasion of deep muscle has probably occurred. Tonsillar lesions that produce trismus or cranial nerve palsy should be classified as T4.

TREATMENT: BASE OF THE TONGUE

Selection of Treatment Modality

Although a few centers continue to recommend glossectomy for selected cases, irradiation is the prescribed treatment in our clinic, and operation is reserved for salvage of radiation therapy failures. Radiation treatment produces better local control rates than surgery, excision of the base of the tongue causes much greater disability than radiation therapy, and the surgeon must deal with a high risk for bilateral neck disease. Radiation therapy automatically encompasses the neck nodes on both sides of the neck, and neck dissection is added following radiation therapy as outlined in Chapter 6.

Extended supraglottic laryngectomy may be used for limited lateralized vallecular lesions, but there are definite criteria that must be satisfied, and this selection limits its usefulness. The following conditions must be met:

- No gross involvement of the pharyngoepiglottic fold
- Preservation of one lingual artery
- Resection of less than 80% of the base of the tongue

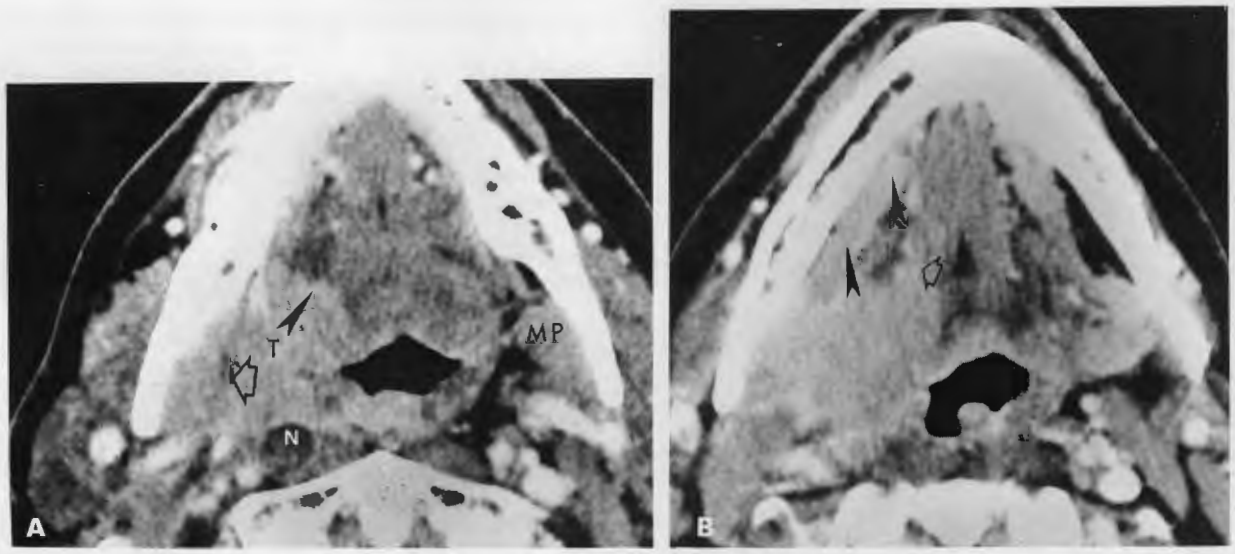


Figure 17-9. A patient with carcinoma of the glossotonsillar sulcus and base of the tongue. (*A*) At the mid-tonsillar level, tumor (T) spreads to involve the tongue base at its junction with the posterior oral tongue (*arrowhead*). Posterolaterally, it completely obliterates the parapharyngeal space and extends laterally to invade the medial pterygoid muscle (*open arrow*); compare these findings to the opposite normal parapharyngeal space and medial pterygoid muscle (MP). Spread to the infratemporal fossa and masticator space can be only suggested clinically, and MRI or CT will frequently show such infiltration in the absence of obvious trismus or a definitely palpable deep mass. Also note the positive retropharyngeal node (N). (*B*) At the level of the circumvallate papillae, the infiltrating mass in the glossotonsillar sulcus spreads anteriorly along the mylohyoid muscle (*arrowheads*) and within the sublingual space. Such anterior spread sometimes cannot be detected even with bimanual palpation. Note the infiltration along the lingual vessels manifested by the obliteration of the tissue planes around the vessels (*open arrow*). The indistinct margins and tendency to perineurovascular spread indicate an aggressive tumor.

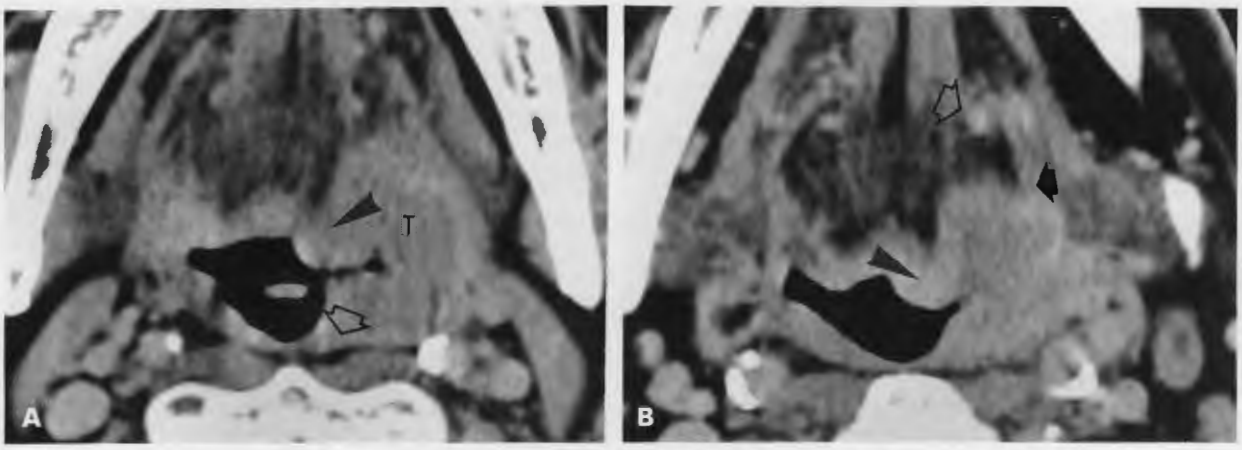


Figure 17-10. A man with carcinoma of the left glossotonsillar sulcus and tongue base. (*A*) Section made at the circumvallate papillae level shows a well-circumscribed tumor (T) extending near the midline both in the tongue (*arrowhead*) and along the posterior pharyngeal wall (*open arrow*). (*B*) A section 1 cm below *A* demonstrates the difficulty in differentiating tumor from normal lingual tonsil (*arrowhead*); however, there is no extension across the midline within the intrinsic tongue muscles. Note the thickening of the hyoglossus muscle (*solid arrow*) and the subtle obliteration of tissue planes around the lingual vessels (*open arrow*) compared with the opposite side. This pattern is consistent with spread of tumor along the hyoglossus muscle and lingual vasculature.

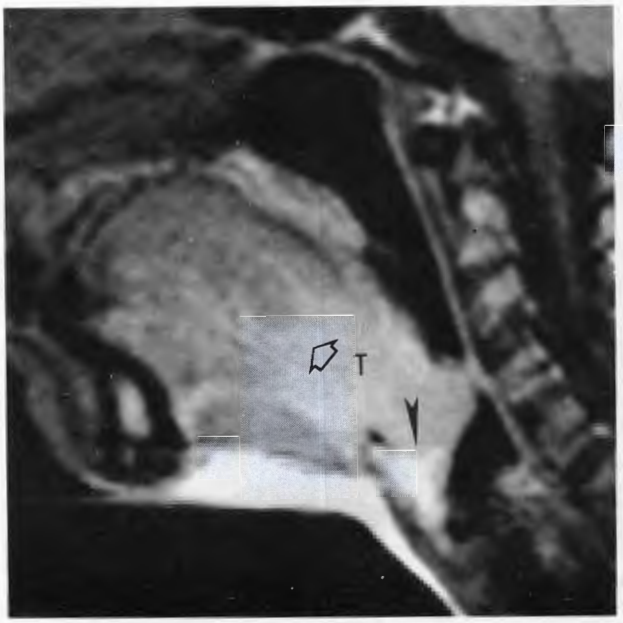


Figure 17-11. A patient presented with a 1-year history of progressive otalgia. Inspection and palpation of the base of the tongue at another institution revealed no obvious mass. A CT study at another institution 1 month before referral was reportedly negative. An MRI study shows an infiltrating tumor (T) extending into the tongue base (*open arrow*) and growing inferiorly toward the preepiglottic space (*arrowhead*). Biopsy revealed squamous cell carcinoma.

- Pulmonary function suitable for supraglottic laryngectomy
- Medical condition suitable for a major operation

At least an ipsilateral neck dissection is indicated; but with the high risk of bilateral neck disease even in the patient with no node involvement, this represents incomplete treatment. Finally, the surgeon has difficulty determining tumor extent in the tongue at the time of excision. Postoperative radiotherapy may have to be administered in any event for close margins or for fear of recurrence in the neck.

Surgical Treatment

Operation is best suited for well-lateralized lesions with minimal neck disease. An anterior lesion may be resected leaving the larynx intact, while a posterior lesion may require the addition of supraglottic laryngectomy. The surgical approach for small neoplasms of the base of the tongue is either by splitting the lip, mandible, and oral tongue in the midline to reach the tongue base or by dividing the mandible near the angle and approaching the base of the tongue from the side. After the tumor has been removed, the mandible is wired together. Splitting the mandible after irradiation, however, produces a higher risk of osteoradionecrosis. Another technique for removal of tumors at the base of the tongue involves the "floor drop" procedure. This surgical technique involves elevation of the inner periosteum from the mandible, usually from angle to angle. Care must be taken to preserve one facial artery. The entire floor of mouth and tongue are then "dropped" into the neck, exposing the base of the tongue and the tumor. After the tumor has been excised, the defect can be repaired with either a skin graft, a lingual flap, or a myocutaneous flap. We prefer a skin graft whenever possible because a flap is usually too bulky and interferes with good lingual function for speech and swallowing. There have been no instances of osteoradionecrosis in 12 patients who have had this procedure for recurrence after radiation therapy.

Irradiation Technique

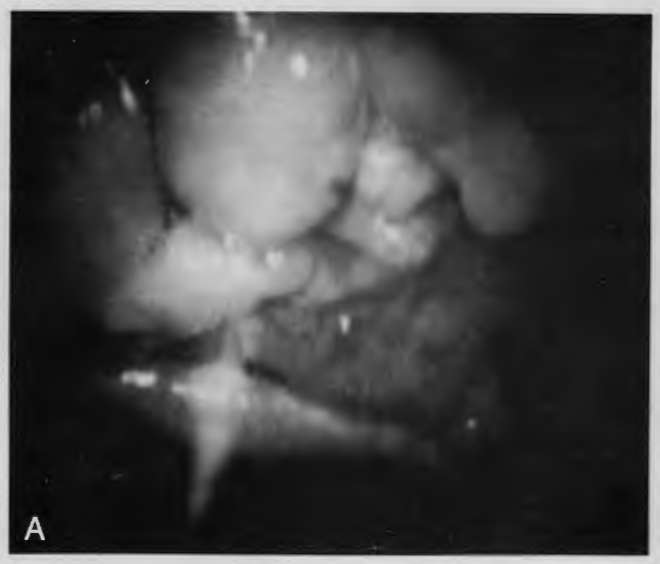
The irradiation of cancer of the base of the tongue is basically accomplished by parallel opposed external-beam portals, which also encompass the regional lymph nodes on both sides. The risk of lymph node metastases in both the upper and lower neck is significant, and the entire neck on both sides is routinely treated even when the neck is clinically free of disease. The usual initial treatment volume includes the base of the tongue, vallecculae, suprahyoid epiglottis, upper portion of the preepiglottic space, pharyngeal walls, and varying amounts of the oral tongue, depending on the anterior extent of disease; the internal jugular chain and junctional and spinal accessory nodes on both sides are encompassed up to the base of the skull.[29] The lower border of the primary treatment field is the thyroid notch unless tumor extends into the supraglottic larynx, hypopharynx, or preepiglottic space. The skin and subcutaneous tissues in the submental midline are shielded unless the patient is very thin or tumor extends into the submental area. The spinal cord is shielded from the treatment volume after 4500 to 5000 cGy is administered over 5 weeks.

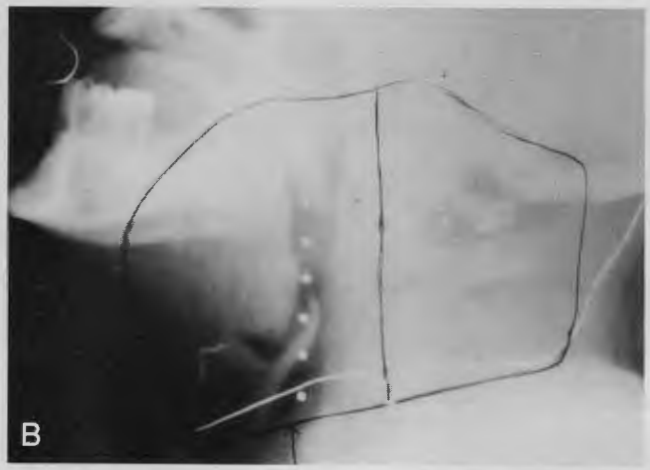
One of the common errors in planning therapy using external-beam portals is failure to recognize anterior growth of the neoplasm as determined by palpation through the lateral floor of the mouth. If not palpable, this can be visualized on CT or MRI. Such spread *can* be subtle and manifest only by obliteration of tissue planes surrounding the lingual neurovascular bundle. The use of long lateral primary fields that include the larynx and a longer length of spinal cord than necessary is inappropriate. It is essential to divide the treatment volume into upper (primary) and anterior low-neck fields so that the larynx can be shielded and the length of spinal cord and pharyngeal wall irradiated is reduced; this division is important even in the presence of a large lymph node that is bisected by the junction. While some radiation oncologists explain that it is acceptable to irradiate the larynx to 5000 cGy because "it can tolerate it," there is little excuse for irradiating a vital structure to a moderately high dose when it is avoidable. Inclusion of the larynx and additional pharyngeal wall within the primary portals causes additional mucosal reaction, which often leads to unplanned treatment interruptions or requires treatment with low total daily doses, either of which results in poor tumor control.[24]

Even small, well-lateralized lesions of the base of the tongue will spread to the opposite neck, and the entire neck on both sides is always treated. The initial primary portals include the upper internal jugular, posterior submandibular, junctional, and spinal accessory lymph nodes (Figs. 17-12 and 17-13).[28] The superior border is 2 to 3 cm above the tip of the mastoid to ensure coverage of the nodes near the base of skull. The lower neck nodes on both sides are always treated. See Chapter 6 for a discussion of neck management.

A boost dose of 500 to 1500 cGy may be delivered to

Figure 17-12. Radiation treatment technique for carcinoma of the base of the tongue. Superiorly, the portal treats the jugular and spinal accessory lymph nodes to the base of skull. The posterior border is behind the spinous process of C2. The inferior border is at or just below the thyroid notch, depending on disease extent. Anteroinferiorly, the skin and subcutaneous tissues of the submentum are shielded, except in the case of advanced disease. The anterior tongue margin is set by palpation. Placing a small stainless-steel pin in the anteriormost extent of palpable disease is useful for identification on simulation film. If tumor is too posterior to pin, the point at which the anterior tonsillar pillar inserts into the tongue is pinned for orientation purposes. Two portal reductions are shown. (Parsons JT, Million RR. Treatment of tumors of the oropharynx: radiation therapy. In: Thawley SE, Pange WR, eds. Comprehensive management of head and neck tumors, vol 1. Philadelphia, WB Saunders, 1987:689)





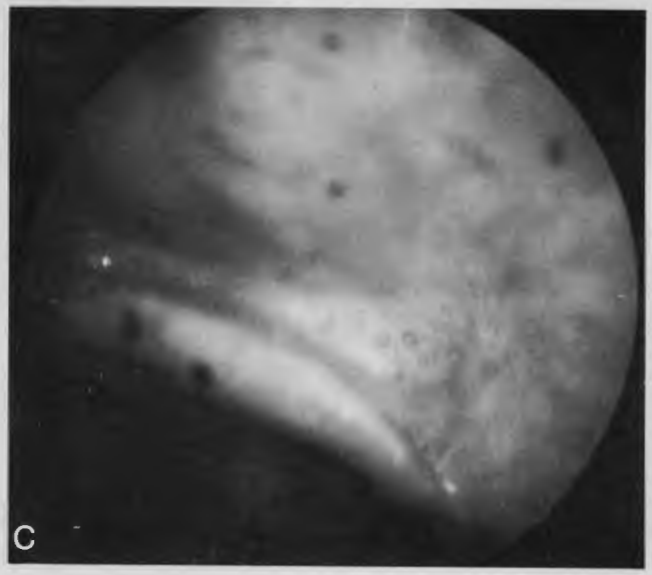


Figure 17-13. Poorly differentiated squamous cell carcinoma of the base of the tongue. (*A*) A 2.5-cm midline tumor of the base of the tongue. There was a 3.0-cm right subdigastric positive lymph node. The patient had a short thick neck that was difficult to evaluate (T2N1). (*B*) Simulator planning film. The base of tongue mass is easily seen; the vallecula is spared. The initial treatment portal is outlined for preparation of a beam-shaping block made of Lipowitz's metal. After 4500 cGy, the portion of the portal behind the cervical bodies is eliminated from the photon fields and a new block is made. Treatment is completed to the posterior section ("posterior strip") with electrons. Treatment to the base of the tongue was continued to 7000 cGy over 7 weeks through lateral portals; a 500-cGy submental boost was added with 17-MeV electrons. (*C*) No disease was evident at 3 years 6 months.

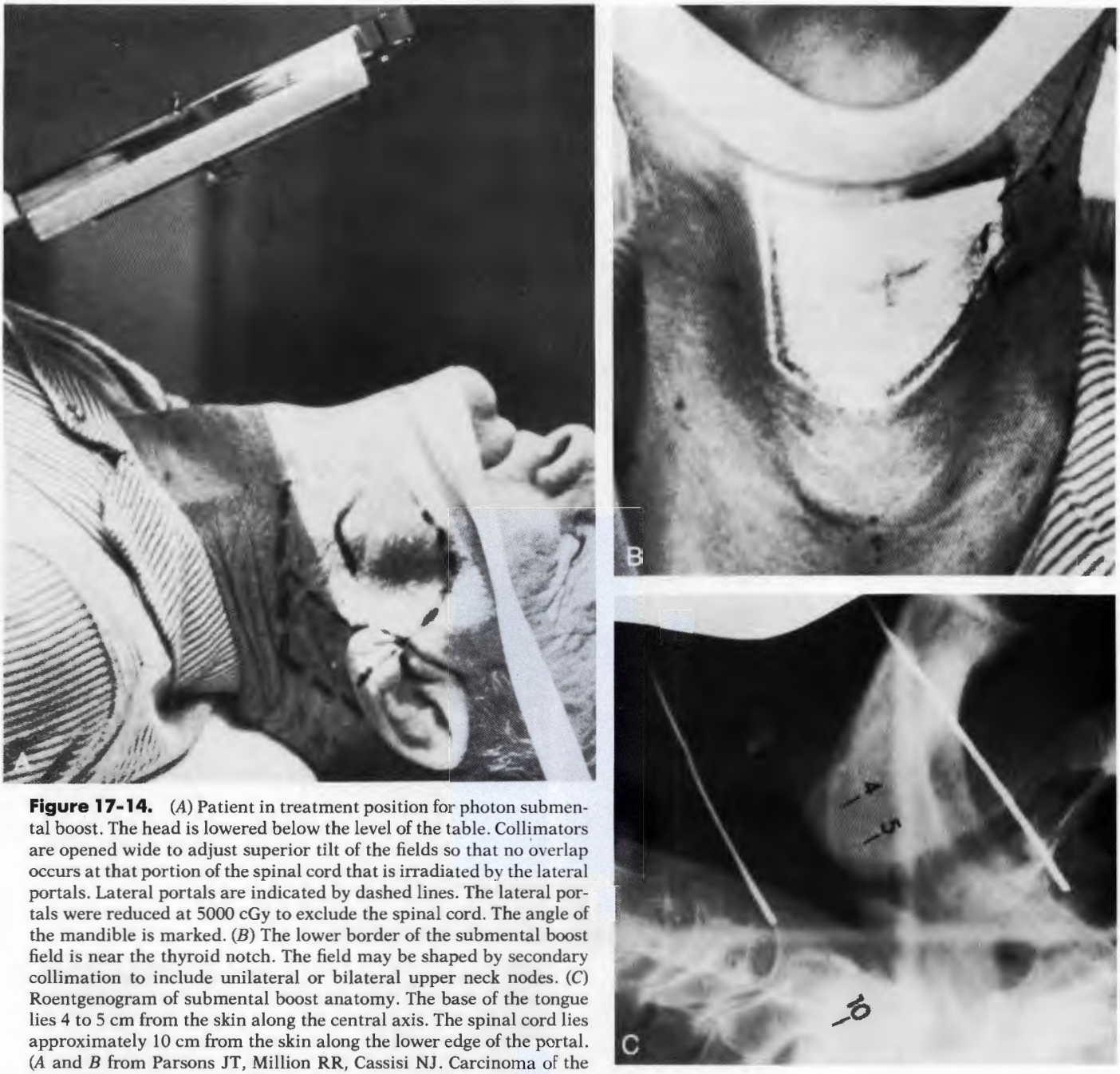


Figure 17-14. (*A*) Patient in treatment position for photon submental boost. The head is lowered below the level of the table. Collimators are opened wide to adjust superior tilt of the fields so that no overlap occurs at that portion of the spinal cord that is irradiated by the lateral portals. Lateral portals are indicated by dashed lines. The lateral portals were reduced at 5000 cGy to exclude the spinal cord. The angle of the mandible is marked. (*B*) The lower border of the submental boost field is near the thyroid notch. The field may be shaped by secondary collimation to include unilateral or bilateral upper neck nodes. (*C*) Roentgenogram of submental boost anatomy. The base of the tongue lies 4 to 5 cm from the skin along the central axis. The spinal cord lies approximately 10 cm from the skin along the lower edge of the portal. (*A* and *B* from Parsons JT, Million RR, Cassisi NJ. Carcinoma of the base of the tongue: results of radical irradiation with surgery reserved for irradiation failure. Laryngoscope 1982;92:691)

the base of the tongue by way of reduced lateral portals or through the submental route. The submental boost technique reduces the dose to the mandible. The submental boost may be given with either high-energy electrons or a photon beam aimed superiorly to avoid the previously irradiated spinal cord (Fig. 17-14). The submental boost is selected for those base of tongue lesions that are central and posterior. Lateralized lesions that involve the glossotonsillar sulcus and lie immediately adjacent to the mandible are not suitable for the submental boost. Large lesions that extend into the oral tongue are not suitable for the submental boost, since the distance from the skin to the tongue surface is greater than 6 cm and the portal is inefficient; an interstitial boost or reduced lateral portals are used for the final dose in these cases.

Interstitial implants are used for part of the treatment at the University of Florida only if the lesion is small, discrete, and located in the anterolateral base of the tongue. Implants of posterior lesions are technically difficult; these implants are usually accomplished with a flexible source (eg, iridium-192 ribbons) that allow through-and-through implantation from the base of the tongue to the skin.

Iridium-192 implants are a popular boost technique in some centers. Local control rates following continu-

ous-course external-beam therapy alone at the University of Florida and at M. D. Anderson Hospital were compared with the results from five centers in which iridium-192 implants were used. There is no convincing evidence that the implant produces superior local control rates or reduced complications compared with external-beam irradiation alone.[13]

A time–dose distribution is shown in Figure 12-8. Split-course techniques resulted in poorer local control and are not used. The initial dose per fraction is 180 to 200 cGy; after 5000 cGy the treatment volume is reduced, and the daily fraction is increased to 200 cGy if patient tolerance is satisfactory. Patients have been treated by 120 cGy twice daily with a 4- to 6-hour interval since 1978. The total doses range from 7440 to 8100 cGy. See Figures 6-40, 6-45, and 6-46 for examples of neck dissection following radical irradiation for base of tongue lesions and Figures 6-49*B* and 6-55*A* for a discussion of portal arrangement for neck irradiation.

Combined Treatment Policies

Combined treatment for the primary lesion is rarely selected since combined treatment is not needed for early lesions and an operation for moderately advanced lesions usually implies major functional loss. Few patients are willing to accept the morbidity considering the substantial control rates with irradiation.

Management of Recurrence

For a painful ulcer, only biopsy can distinguish between recurrence and radiation necrosis; general anesthesia is usually necessary to obtain representative tissue. Radiation failures are treated surgically, but salvage is infrequent. At the University of Florida there have been 36 patients with local failure; 11 had a salvage operation, but this was successful in only two. Fletcher reported surgical salvage after radiation failure in 2 of 9 patients with T2 disease, 1 of 13 with T3 disease, and 2 of 15 with T4 disease.[12]

Recurrence of a small, discrete tumor can be treated by a wide local excision. The larger recurrences require either a jaw–tongue–neck resection or glossectomy–laryngectomy.

Patients with surgical failures are rarely salvaged by either an operation or radiation therapy.

RESULTS OF TREATMENT: BASE OF THE TONGUE

Surgical Results

Whicker and coworkers at the Mayo Clinic reported 102 patients selected for curative attempts by operation between 1960 and 1967.[46] Of 23 who received preoperative or postoperative radiation therapy, 5 survived for 5 years. Of 11 operated on for irradiation failure, 3 survived for 5 years. Twenty-two had radiation salvage attempted after surgical failure, but only 1 survived 5 years. Twenty-three percent required partial or total laryngectomy. Fifty-six patients had positive nodes in the specimen; 22 patients developed delayed appearance of neck metastasis. Only 7% had bilateral pathologically positive nodes at the initial operation. The operative mortality rate was 4%, with a 27% local recurrence rate and 10% neck failure rate with the primary lesion controlled.

Irradiation Results

The local control for 84 patients treated at the University of Florida between 1964 and 1986 is shown in Table 17-1.[13] The follow-up was 2 to 23 years; no patient was lost to follow-up. There was no difference in local control comparing boost by reduced lateral portals and the submental boost. The local control rates for the twice-a-day fractionation scheme were updated by Parsons: T1, 2 of 2 patients; T2, 13 (93%) of 14 patients; T3, 14 (78%) of 18 patients; and T4, 5 (38%) of 13 patients (Parsons JT, unpublished study, March 1991).

Eighty-eight percent of N0–N1 necks and 79% of N2–N3 necks were treated successfully by irradiation with or without planned neck dissection. Five-year rates of continuous disease control above the clavicles were as follows: stages I and II, 100% (8 patients); stage III, 72% (23 patients); stage IVA, 78% (18 patients); stage IVB, 44% (35 patients). Five-year absolute and relapse-free survival rates for the entire group were 43% and 58%, respectively.[13]

Five series reported in 1987–1988, in which the final boost was administered by interstitial implant, are summarized in Table 17-2, along with results from the M. D. Anderson Hospital and the University of Florida, where similar techniques of external-beam irradiation alone

TABLE 17-1. Base of Tongue: Local Control Following Continuous-Course External-Beam Irradiation (84 Patients)

Stage	No. Patients	Excluded*	Fractionation		Local Control After Radiation Therapy Alone
			Once Daily	Twice Daily	
T1	9	5	2/3	1/1	3/4
T2	30	5	15/18 (83%)	7/7 (100%)	22/25 (88%)
T3	31	5	14/18 (78%)	6/8 (75%)	20/26 (77%)
T4	14	0	1/6 (17%)	4/8 (50%)	5/14 (36%)

* Dead of intercurrent disease or metastases less than 2 years after initiation of treatment with primary tumor continuously controlled.

(Modified from Foote RL, Parsons JT, Mendenhall WM, Million RR, Cassisi NJ, Stringer SP. Is interstitial implantation essential for successful radiotherapeutic treatment of base of tongue carcinoma? Int J Radiat Oncol Biol Phys 1990;18:1295)

TABLE 17-2. Base of Tongue: Local Control("Local Nonfailure") and Complications Following Curative Irradiation (Literature Review)

Author, Year, Institution	Boost Technique	Local Control* by T Stage				Incidence of Soft Tissue and/or Bone Necrosis (all Degrees of Severity)
		T1	T2	T3	T4	
Housset et al, 1987[18] Hôpital Necker Paris, France	Implant	6/6	17/23 (74%)	No data	No data	3/29 (10%)
Puthawala et al, 1988[33] Memorial Medical Center Long Beach, California	Implant	2/2	14/16 (88%)	30/40 (75%)	8/12 (67%)	10/70 (14%)
Crook et al, 1988[8] Hâpital Henri Mondor Creteil, France	Implant	11/13 (85%)	25/35 (71%)	No data	No data	12/48 (25%)
Lusinchi et al, 1988[22] Institut Gustave Roussy Paris, France	Implant	15/18 (83%)	20/39 (51%)	35/51 (69%)	No data	29/108 (27%)
Sessions et al, 1988[38] Memorial–Sloan Kettering New York City	Implant	4/4	5/6 (83%)	5/6 (83%)	1/1	6/17 (35%)
Goffinet et al, 1985[17] Stanford University Stanford, California	Implant	4/5	7/7	9/10 (90%)	5/7	8/29 (28%)†
Spanos et al, 1976[41] M. D. Anderson Hospital Houston, Texas	External beam	29/32 (91%)	35/49 (71%)	50/64 (78%)	15/29 (52%)	15/91 (16%)‡
Foote et al, 1990[13] University of Florida Gainesville, Florida	External beam	8/9 (89%)	27/30 (90%)	25/31 (81%)	5/14 (36%)	19/84 (23%)

* No. patients continuously free of disease at the primary site/total number treated.
† Three patients who developed hemorrhage are included.
‡ Bone only.
(Foote RL, Parsons JT, Mendenhall WM, Million RR, Cassisi NJ, Stringer SP. Is interstitial implantation essential for successful radiotherapeutic treatment of base of tongue carcinoma? Int J Radiat Oncol Biol Phys 1990;18:1297)

were used. Since there are some differences in the manner in which local control rates were calculated for the former five implant series and the latter two from the M. D. Anderson Hospital and University of Florida, results have been recalculated for this table by the same method used in the implant series, so that they will be directly comparable (ie, local control = total number of patients who remained continuously free of disease at the primary site divided by the total number of patients treated). Table 17-3 sums the data from the various series. It would be difficult to use these data to argue for the superiority of the implant in terms of local control. The only subgroup for which there appeared to be superiority of the implant was T4, and only a select group of T4 patients would be suitable for implant.[13] The interstitial technique is technically complicated, adds considerably to the expense of the treatment course, and may be attended by brisk bleeding at the time of implant removal that is sometimes life-threatening (Goffinet DR, personal communication, September 1988).[17,29] The implant usually requires general anesthesia at least once and sometimes twice,[29] usually requires tracheotomy, sometimes leads to severe complications such as septicemia (Goffinet DR, personal communication, September 1988)[17] or aspiration pneumonia,[29] and is not applicable to some patients with preexisting medical problems. The implant is not well suited to all T4 lesions.

Combined Treatment

There are few data regarding combinations of surgery and irradiation for carcinoma for the base of tongue. In 1985, Goffinet and associates reported on 14 patients from Stanford University who underwent radical resection plus 5000 to 6600 cGy postoperatively. Eleven of the patients had stage II or III disease. The 2-year relapse-free survival rate was 36%; four of the five survivors suffered debilitating complications (unintelligible speech, inability to swallow, fistulae, wound breakdown, necrosis, and/or esophageal stricture).[17]

TABLE 17-3. Base of Tongue: Local Control ("Local Nonfailure") Rates by T Stage Following External-Beam Irradiation Alone Versus External Beam Plus Implant*

Treatment Technique	T Stage			
	T1	T2	T3	T4
External beam†	37/41 (90%)	62/79 (78%)	75/95 (79%)	20/43 (47%)
External beam plus implant	42/48 (88%)	88/126 (70%)	79/107 (74%)	14/20 (70%)

* Data from six series (see text), compiled from Table 17-2.

† University of Florida and M. D. Anderson Hospital data.

(Foote RL, Parsons JT, Mendenhall WM, Million RR, Cassisi NJ, Stringer SP. Is interstitial implantation essential for successful radiotherapeutic treatment of base of tongue carcinoma? Int J Radiat Oncol Biol Phys 1990;18:1298)

COMPLICATIONS OF TREATMENT: BASE OF THE TONGUE

Surgical Complications

The complications of surgery include an operative mortality of about 5%; other complications include fistula, mandibular necrosis, dysarthria, dysphagia, hoarseness, trismus, and carotid rupture.

Complications of Irradiation

The risk of radiation therapy complications by boost technique and fractionation schedule is shown in Tables 17-4 and 17-5.[13] A self-healing soft tissue necrosis of less than 6 months' duration occurred in 15% and required more than 6 months to heal in 5% of patients. Self-healing bone exposure occurred in 5%, and a single patient required an operation for bone necrosis. Moderate and severe complications were not observed in 25 stage T2–T4 patients treated twice a day. An update of the patients treated twice a day showed one severe complication in 44 patients treated (Parsons JT, unpublished study, March 1990). Treatment of necrosis requires patience and reassurance to the patient, who assumes the pain is due to cancer. Antibiotics will often reduce pain. The patient may lose weight because of dysphagia and require nutritional support. Hemorrhage is rare.

Hypoglossal nerve palsy occurred in two patients and is reported in other series. Unilateral hypoglossal nerve palsy does not produce serious morbidity because the opposite side compensates rather well. Infrequent complications include mild trismus and otitis media. An occasional patient cured by radiation therapy of advanced cancer of the base of the tongue may have difficulty swallowing solid foods. The action of the base of the tongue is to force the bolus of food into the hypopharynx, and loss of full motion impedes swallowing. The dysphagia is probably a result of some fibrosis of the base of the tongue and pharyngeal constriction, compounded by a dry mouth. Aspiration is unusual, however, even if the tip of the epiglottis has been amputated by tumor.

Complications of Combined Treatment

Preoperative irradiation will increase the risk of fistula, delayed healing, and carotid exposure.

Postoperative irradiation increases the amount of fibrosis in the neck. Radiation necrosis of the soft tissues or bone may occur. The added effect of xerostomia further worsens the swallowing defect produced by glossectomy.

TREATMENT: TONSILLAR AREA

Selection of Treatment Modality

Early Lesions (T1–T2)

Early lesions are treated by irradiation with a high rate of success and relatively little morbidity; a neck dissection may be added after radiation therapy, as outlined in Chapter 6. An occasional small superficial, dis-

TABLE 17-4. Base of Tongue: Bone Exposure and Soft Tissue Necrosis According to Boost Technique*

Boost Technique (No. Patients)	Bone Exposure			Soft Tissue Necrosis		
	Mild	Moderate	Severe	Mild	Moderate	Severe
Lateral (50)	1 (2%)	0 (0%)	1 (2%)	6 (12%)	1 (2%)	0 (0%)
Submental (34)	2 (6%)	1 (3%)	0 (0%)	6 (18%)	3 (9%)	0 (0%)
Total (84)	3 (4%)	1 (1%)	1 (1%)	12 (14%)	4 (5%)	0 (0%)

* Two patients who developed both bone exposure and soft tissue necrosis were scored twice.

(Foote RL, Parsons JT, Mendenhall WM, Million RR, Cassisi NJ, Stringer SP. Is interstitial implantation essential for successful radiotherapeutic treatment of base of tongue carcinoma? Int J Radiat Oncol Biol Phys 1990;18:1296)

TABLE 17-5. Bone Exposure and Soft Tissue Necrosis According to Fractionation Schedule*

Fractionation (No. Patients)	Bone Exposure			Soft Tissue Necrosis		
	Mild	Moderate	Severe	Mild	Moderate	Severe
Once-a-day (59)	2 (3%)	1 (2%)	1 (2%)	7 (12%)	4 (7%)	0 (0%)
Twice-a-day (25)	1 (4%)	0	0	5 (20%)	0	0 (0%)
Total (84)	3 (4%)	1 (1%)	1 (1%)	12 (14%)	4 (5%)	0 (0%)

* Two patients who developed both bone exposure and soft tissue necrosis were scored twice.
(Foote RL, Parsons JT, Mendenhall WM, Million RR, Cassisi NJ, Stringer SP. Is interstitial implantation essential for successful radiotherapeutic treatment of base of tongue carcinoma? Int J Radiat Oncol Biol Phys 1990;18:1297)

crete lesion of the anterior tonsillar pillar is managed by wide local excision. A surgical attack usually implies removal of the mandible, the tonsillar area including both pillars and part of the soft palate, and perhaps part of the tongue; additionally, an ipsilateral neck dissection is performed even with a clinically negative neck. The functional loss is not justified in view of the high success rate with irradiation, which leaves the patient intact; even a dry mouth may be avoided when well-lateralized lesions are treated by techniques that allow at least partial salivary recovery. An operation will often salvage the few patients with recurrence after radiation treatment.

Moderately Advanced Lesions (T2–T3)

Radiation therapy with or without planned neck dissection is selected as the initial therapy with operation reserved for radiation failures. Local failure with radiation therapy occurs more often for lesions arising from the anterior tonsillar pillar than for those of the tonsillar fossa. Preoperative irradiation followed by an operation has not shown any improvement in the cure rate compared with radical radiation therapy with surgical salvage.[31,43,44] Surgical salvage is more likely to succeed for anterior tonsillar pillar recurrences than for tonsillar fossa recurrences.

Advanced Lesions (T4)

If the lesion is assigned to stage T4 only because of mandible invasion, then an operation followed by radiation therapy should be advised. Radical irradiation will locally control about 36% of advanced (T4) lesions with continuous-course, once-a-day fractionation and 55% with twice-a-day fractionation (see Chap. 12).

Surgical Treatment

Surgical treatment for early cancers of the tonsillar pillar (less than 1 cm in size) consists of a wide local excision through a transoral approach. Occasionally, larger lesions of the tonsil with extension into the base of the tongue can be approached by splitting the mandible anterior to the mental foramen and rotating the mandible laterally. This allows access to the tonsil, tongue base, and lateral pharyngeal wall. This approach (mandibular swing) can only be done if the lesion is not adjacent to the mandible or the inner periosteum of the mandible.

Larger lesions require removal of the adjacent mandible as well as a portion of the tongue and soft palate. Depending on the size of the defect, a skin graft or a tongue or myocutaneous flap may be required to close the defect. Flaps are usually necessary for extensive lesions or for salvage operations after failure of radiation therapy. Deglutition is often a problem, and some patients remain on liquid diets. Chewing is difficult since a portion of the mandible has been removed, and the patient is unable to wear dentures. Speech will probably be impaired if a portion of the tongue or palate has been removed.

Irradiation Technique

Discrete lesions of the anterior tonsillar pillar may be suitable for a portion of the treatment to be given by intraoral cone. A dose of 500 to 1500 cGy is given before external-beam therapy. Daily doses of 250 to 275 cGy are usually selected. The minimum initial external-beam treatment volume for early cancers of the tonsillar region includes the retromolar trigone, tonsillar fossa and pillars, adjacent soft palate and tongue, and the upper neck nodes. The anterior margin of the portal varies according to the anterior extent of disease; in early cases, it is at the level of the third molar tooth. If the buccal mucosa is invaded, anterior coverage should be generous for the first 5000 cGy to avoid geographic miss. Anterior extension into the oral tongue is determined by digital palpation and marked by inserting a small pin with the use of local anesthesia (see Chap. 14).

The basic portal arrangement depends on the extent of the local lesion and the presence or absence of positive lymph nodes. The risk for contralateral lymph node metastasis is small unless there is tongue invasion, invasion of the soft palate near the midline, or clinically positive nodes in the ipsilateral neck. If these risk features are absent, an ipsilateral portal with a combination of photons and electrons that partially spares the contralateral mucosa and salivary glands may be used (Fig. 17-15). The major advantage of these techniques is not a greater cure rate but a lower incidence of xerostomia as a result of partial preservation of minor and major salivary gland function on the contralateral side. An intraoral lead block is often added, which further protects the contralateral minor salivary glands and a portion of the parotid. Since the lesions lie behind the dense mandible, an extra 1.0 to 1.5 cm is added to the depth–dose calcula-

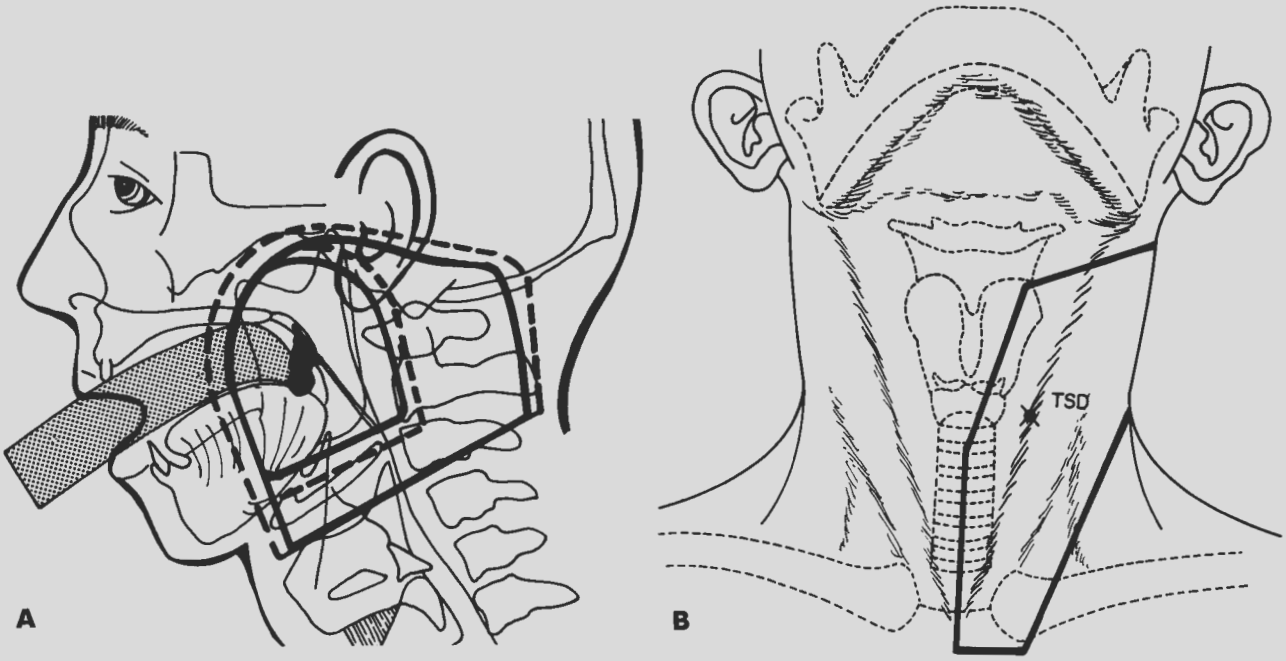


Figure 17-15. "Mixed beam" irradiation portals for tonsillar cancer. (*A*) Early lesions of the tonsillar region that do not extend near the midline may be treated by an ipsilateral technique using both high-energy electron and high-energy x-ray treatments. The advantage of the technique is the delivery of a low dose to the contralateral parotid gland and contralateral mucosal surfaces. An intraoral lead block further reduces the irradiation dose to contralateral mucosa and shields some minor salivary glands from the beam. Because of constriction of the effective treatment area with electrons compared with x-rays, the perimeter of the electron beam portals (*dashed lines*) is larger by 1 cm, except at the inferior border, which adjoins the lower neck field. Because these lesions lie behind the dense mandible, 1.0 to 1.5 cm is added for depth dose calculations for the electron portion of the treatment to compensate for shadowing of the tumor by the mandible. (*B*) Portal used to irradiate the neck in conjunction with mixed-beam therapy to the primary tumor. If the neck is not involved clinically, only the ipsilateral nodes require irradiation (5000 cGy at D_{max} [given dose] in 25 fractions or 4050 cGy in 15 fractions). TSD, tumor-to-source distance. (Parsons JT, Million RR. Treatment of tumors of the oropharynx: radiation therapy. In: Thawley SE, Panje WR, eds: Comprehensive management of head and neck tumors, vol 1. Philadelphia, WB Saunders, 1987:692)

tions for the electron portion of the treatment (see Chap. 14).

If high-energy electrons or photons are not available, a wedge pair may be used. We have generally not used wedges because of inability to shape the fields and the possibility of geographic miss and because it is more difficult to match the low neck portal to the primary portal than when direct lateral portals are used. Lesions with a risk for bilateral neck disease or with extension of the primary lesion beyond 4-cm depth are treated with parallel opposed photon portals, usually weighted 2:1 or 3:2 to the involved side; if there are positive contralateral nodes or extension across the midline, the portals are equally weighted.

The pterygoid plates up to the base of the skull should be covered in advanced cases; if trismus is present, the pterygoids should remain within the treatment volume for the entire course of irradiation. Nasopharyngeal or hypopharyngeal extension must be recognized in order to avoid geographic miss with the reduced fields.

When there is invasion of the adjacent tongue, an additional boost dose of 1000 to 1500 cGy is usually added by an interstitial implant confined to the residual disease. The implant is normally added even if the tongue disease has disappeared during the treatment course. If there is still palpable nodularity in the tonsillar fossa following external-beam irradiation, the pterygoid region is also implanted (Fig. 17-16).

A time–dose analysis for local control is shown in Figure 12-7. Nearly all T1 and T2 tonsillar fossa lesions are locally controlled with doses of 6000 cGy over 6 weeks to 6600 cGy over 6½ weeks. For T1 and T2 anterior tonsillar pillar lesions, however, there is a 20% to 30% local failure rate, unrelated to total dose. The reason for the disparity in local control rates between these two adjacent sites is not known.

For carcinomas of the tonsillar pillar, we are exploring the use of treatment schemes employing iridium hairpin implant boosts, as pioneered by Pierquin.[8] In selected early tonsillar pillar lesions, the dose may be boosted through intraoral cone irradiation rather than by implant.

Twice-daily fractionation schemes, 120 cGy with a 4- to 6-hour interval, have produced no improvement in local control rates compared to once-a-day schemes at the University of Florida, but the twice-a-day treatment does have the advantage of reduced late morbidity. The dose for T2 to T4 lesions since 1978 has varied from 7440 to 8100 cGy, and boost implants have been added as outlined earlier. There has been no correlation between

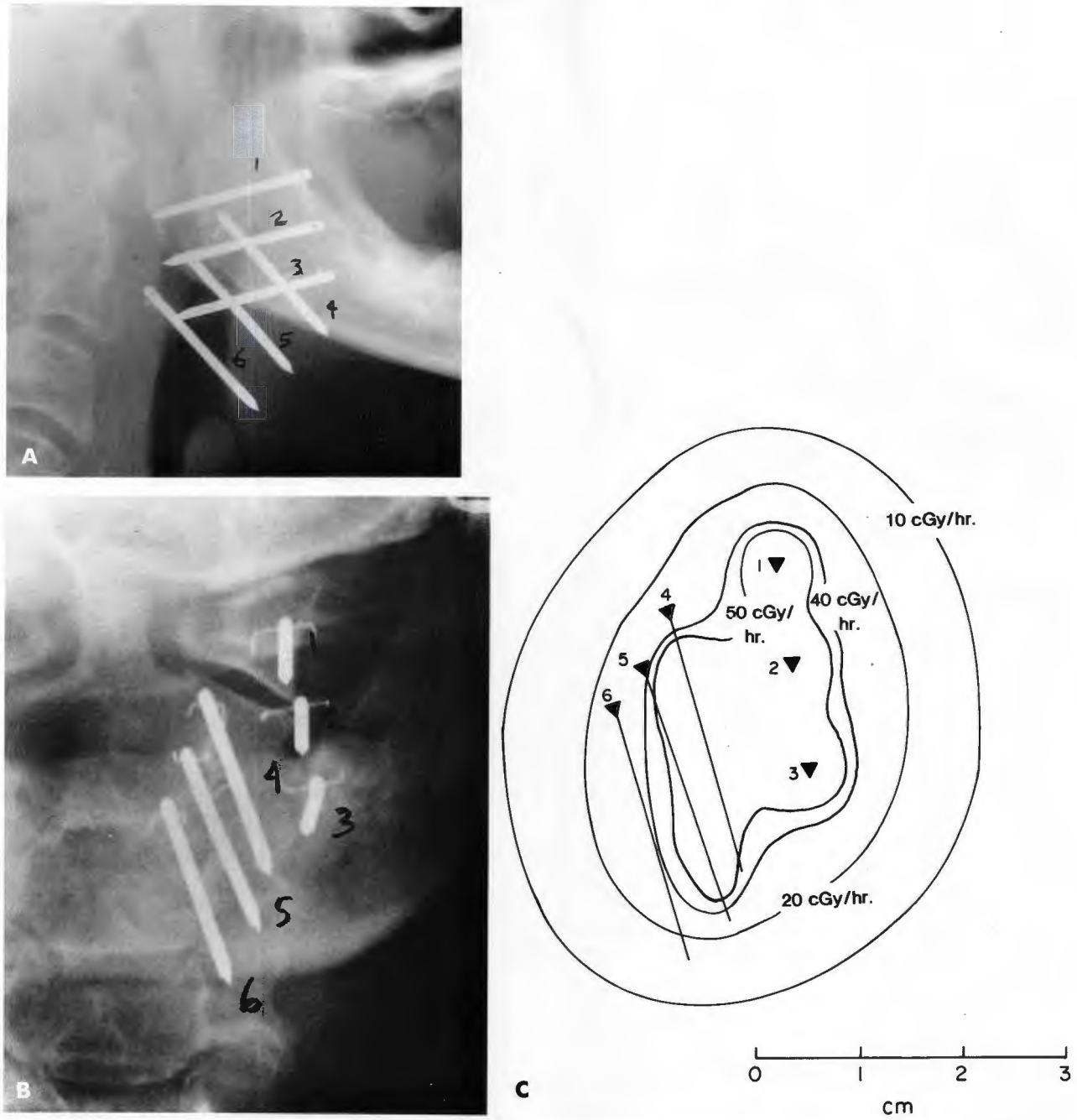


Figure 17-16. Lateral (*A*) and anteroposterior (*B*) radiographs of a tongue–pterygoid implant used to boost the dose to the tumor in the tonsillar fossa and base of tongue after external beam irradiation. Three radium (or cesium) needles (2.0 cm active length, 3.2 cm actual length) are attached to each of two rigid (nylon) implant devices (not visible). The use of rigid implant devices shortens the overall operating time, ensures adequate spacing between needles, and helps make the planes parallel. The approach to pterygoid implantation (needles 1 to 3) is through the lateral floor of the mouth; the needles are inserted perpendicularly through the mucosa between the retromolar trigone and the free edge of the anterior tonsillar pillar, entering the region of the internal pterygoid muscle and parapharyngeal and pterygomandibular spaces. The plane of needles in the base of tongue (needles 3 to 6) is approximately 1.0 cm medial to that in the pterygoid region. Usually no crossing needles are required. The bars are sutured into place with 2-O silk, and anteroposterior and lateral radiographs are obtained to verify proper positioning of the needles before the patient leaves the operating room. (*C*) Orthogonal radiographs are obtained on the way from the recovery room to the patient's room. Computer dosimetry is performed. The orientation of the dosimetry is as shown in the anteroposterior view in Figure 17-18*B*. The plane of calculation is perpendicular to and through the middle of needle 2. A dose of 1500 cGy is delivered to the 40-cGy/h line (implant time: 37.5 hours). Implanted needles are removed in the patient's room. (Parsons JT, Million RR. Treatment of tumors of the oropharynx: radiation therapy. In: Thawley SE, Panje WR, eds. Comprehensive management of head and neck tumors, vol 1. Philadelphia, WB Saunders, 1987:693)

TABLE 17-6. Local Control as a Function of Tonsillar Region Site* (No. Controlled/No. Treated)

T Stage	Excluded†	Tonsillar Fossa	Anterior Tonsillar Pillar	Posterior Tonsillar Pillar	Overall Control with Irradiation	No. Salvaged/ No. Attempted	Ultimate Control
T1	4	4/4	5/7	1/1	10/12 (83%)	2/2	12/12
T2	9	17/18 (94%)	18/26 (69%)	1/2‡	36/46 (78%)	5/7	41/46 (89%)
T3	8	23/31 (74%)	5/8	No data	28/39 (72%)	0/3	28/39 (72%)
T4	5	3/12 (25%)	2/4	No data	5/16 (31%)	0/1	5/16 (31%)

* Continuous-course, once-a-day fractionation; 110 patients with 113 evaluable primary lesions.

† Patients were excluded from analysis of disease control at the primary site and/or neck if they died within 2 years from treatment with that particular site continuously free of disease.

‡ Failure at 4700 cGy.

(Mendenhall WM, Parsons JT, Cossisi NJ, Million RR. Squamous cell carcinoma of the tonsillar area treated with radical irradiation. Radiother Oncol 1987;10:25)

local control rates and dose within the range of 7440 and 8100 cGy, with or without the implant, when analyzed according to T stage. The entire ipsilateral neck is always electively irradiated, and the opposite neck is electively irradiated when at risk. When clinically positive nodes occur in the ipsilateral neck, the opposite neck is almost always electively treated.

See Chapter 6 for management of neck node metastases.

Combined Treatment Polices

Patients selected for combined treatment preferably have resection first, followed by postoperative irradiation. A large, fixed node is the most common indication for preoperative irradiation.

Management of Recurrence

An operation will salvage a good proportion of T1 or T2 radiation therapy failures, but few patients are salvaged when an advanced lesion recurs (Tables 17-6 and 17-7). A patient with neck recurrence after radiation therapy for clinically involved lymph nodes can only occasionally be salvaged by neck dissection (Table 17-8).

RESULTS OF TREATMENT: TONSILLAR AREA

The results for 136 patients treated by radiation therapy alone (104 patients) or in conjunction with planned neck dissection (32 patients) are shown in Tables 17-6 through 17-10.[23] For patients with a clinically negative neck, the control rate for neck disease was 33 of 34. There was a high rate of intercurrent death (29%) for patients with stages I through III. The overall risk of multiple head and neck primary tumors was 17%.

The local control rates for the group of patients treated twice a day (1978–1989) were, for stage T1, 5 of 5; for stage T2, tonsillar fossa, 9 of 11, and anterior tonsillar pillar, 15 of 21 (71%); for stage T3, 24 of 33 (73%); and for stage T4, 6 of 11 (55%) (Parsons JT, unpublished study, March 1991). These local control rates are nearly identical to those reported for the historical series of patients treated by once-a-day fractionation.

Fourteen patients, usually the less favorable cases, were selected for operation and radiation therapy. Eight were treated with preoperative radiation therapy; 7 developed a local recurrence, and only 1 had no evidence of disease more than 2 years after treatment. Six were treated by resection and postoperative radiation therapy; only 1 developed a local recurrence, and 4 had no evidence of disease more than 2 years after treatment.

TABLE 17-7. Tonsillar Area: Control Above the Clavicles (No. Controlled/ No. Treated)*

Modified AJCC Stage	Excluded†	Control following Initial Treatment	No. Salvaged/ No. Attempted	Ultimate Control
I	4	3/5	2/2	5/5
II	4	20/29 (69%)	4/6	24/29 (83%)
III	3	22/29 (76%)	1/2	23/29 (79%)
IVA	4	13/22 (59%)	1/4	14/22 (64%)
IVB	7	13/29 (45%)	1/4	14/29 (48%)

* 114 evaluable patients.

† Patients were excluded from analysis of disease control at the primary site and/or neck if they died within 2 years from treatment with that particular site continuously disease-free.

(Mendenhall WM, Parsons JT, Cassisi NJ, Million RR. Squamous cell carcinoma of the tonsillar area treated with radical irradiation. Radiother Oncol 1987;10:28)

TABLE 17-8. Tonsillar Area: Control of the Clinically Positive Neck as a Function of Treatment* (No. Heminecks Controlled/No. Treated)

Hemineck Stage	Radiation Therapy Alone	Radiation Therapy Plus Neck Dissection	Overall Control With Initial Treatment	No. Salvaged/ No. Attempted	Overall Ultimate Control
N1	18/18	4/4	22/22	No data	22/22
N2A	1/2	3/4	4/6	0/1	4/6
N2B	9/12	12/12	21/24	1/2	22/24
N3A	0/1	2/3	2/4	No data	2/4

* Primary lesion continuously disease-free; 43 patients with 56 evaluable heminecks. Continuous-course radiotherapy, one fraction per day.
(Mendenhall WM, Parsons JT, Cassisi NJ, Million RR. Squamous cell carcinoma of the tonsillar area treated with radical irradiation. Radiother Oncol 1987;10:27)

TABLE 17-9. Tonsillar Area: Local Control After Initial Treatment for T3 Lesions With Tongue Involvement (No. Controlled/No. Treated)

Primary Site	External Beam Alone	External Beam Plus Implant
Anterior tonsillar pillar	1/2	2/4
Tonsillar fossa	4/7	11/13 (85%)

(Mendenhall WM, Parsons JT, Cassisi NJ, Million RR. Squamous cell carcinoma of the tonsillar area treated with radical irradiation. Radiother Oncol 1987;10:25)

TABLE 17-10. Tonsillar Area: Five-Year Survival by Modified AJCC Stage (No. Alive/No. Treated)*

Modified AJCC Stage	5-Year Absolute Survival	5-Year Cause-Specific Survival
I	3/9	3/3
II	13/22 (59%)	13/14 (93%)
III	14/22 (64%)	14/17 (82%)
IVA	6/17 (35%)	6/14 (43%)
IVB	4/24 (17%)	4/19 (21%)

* 94 patients.
(Mendenhall WM, Parsons JT, Cassisi NJ, Million RR. Squamous cell carcinoma of the tonsillar area treated with radical irradiation. Radiother Oncol 1987;10:28)

TABLE 17-11. Carcinoma of the Tonsillar Region: High-Dose Preoperative Irradiation Versus Radiation Therapy ± Neck Dissection (With Surgery Reserved for Salvage After Irradiation Failure)

	5-Year Cause-Specific Survival			
Stage	Preoperative RT (4500–5000 cGy) plus TJN (University of Cincinnati)[16]	Preoperative RT (5000 cGy/5 wk) plus TJN (Syracuse)[34]	Preoperative RT (5000–6000 cGy) plus TJN (Virginia)[15]	RT ± Neck Dissection/Surgical Salvage (University of Florida)[23]
I	3/3	No data	3/3	3/3
II	14/16 (88%)	8/12 (67%)	1/1	13/14 (93%)
III	21/31 (68%)	11/14 (79%)	0/3	14/17 (82%)
IV	8/32 (25%)	8/21 (38%)	3/15 (20%)	10/33 (30%)

TJN, tongue–jaw–neck dissection.
(Modified from Parsons JT, Mendenhall WM, Million RR, Stringer SP, Cassisi NJ. The management of primary cancers of the oropharynx: combined treatment or irradiation alone? Semin Radiat Oncol 1992;2(3):143)

TABLE 17-12. Carcinoma of the Tonsillar Region: Control Above the Clavicles Following High-Dose Preoperative Irradiation Versus Radiation Therapy ± Neck Dissection

	Control Above the Clavicles		
Stage	Preoperative RT (5400 cGy) Plus Surgery University of California (SF)[25] (No Minimum Follow-up)	Preoperative RT (Dose Not Stated) Plus Surgery Mayo Clinic[3] (2 Years' Minimum Fallow-Up)	Radiation Therapy ± Neck Dissection University of Florida[23] (2 Years' Minimum Follow-Up)
I	7/11 (64%)	No data	20/29 (69%)*
I–II	8/12 (67%)	1/5 (20%)	23/34 (68%)†
III–IV	12/18 (67%)	10/14 (71%)	48/80 (60%)‡

Ultimate control (after salvage surgery): * 24/29 (83%); † 29/34 (85%); ‡ 51/80 (64%).
(Parsons JT, Mendenhall WM, Million RR, Stringer SP, Cassisi NJ. The management of primary cancers of the oropharynx: combined treatment or irradiation alone? Semin Rodiat Oncol 1992;2(3):144)

Bataini and associates analyzed 465 patients treated by radiation therapy.[4] They concluded that the treatment course should not extend over more than 35 to 40 days for optimal results and that the overall treatment time was more important than the total dose.

Wong and associates reviewed the M. D. Anderson Hospital results for 150 patients with squamous cell carcinoma of the tonsillar fossa and could not demonstrate a dose response within each T stage.[47] They reported local control rates as follows: T1, 94%; T2, 79%; T3, 58%; and T4, 50%.

The results of irradiation alone and preoperative irradiation are compared in Tables 17-11 through 17-13.[27] Perez and associates updated the St. Louis experience to include 127 patients treated by radiotherapy alone, 133 patients treated by preoperative radiotherapy, and 36 patients treated by postoperative radiotherapy. There was no advantage to combined therapy as compared with irradiation alone.[30]

Spiro and Spiro reviewed the results of treatment of 82 patients with stage III or IV carcinoma of the tonsillar fossa who underwent treatment at Memorial Sloan–Kettering Cancer Center between 1969 and 1983; about one half of the patients were treated with surgical resection plus preoperative or postoperative irradiation.[42] The authors were unable to demonstrate any difference in the 3-year, cause-specific, disease-free survival rates for patients who received combined treatment to the primary site and those treated with irradiation with or without neck dissection.

TABLE 17-13. Carcinoma of the Tonsillar Region: Comparison of NED Survival Rates Following Low-Dose Preoperative Irradiation Versus Radiation Therapy (Mallinckrodt)[31]

	Absolute NED Survival at 3 Years	
Stage	Preoperative Irradiation* Plus Composite Resection	Irradiation† ± Neck Dissection
I, II	11/17 (65%)	16/21 (76%)
III, favarable IV	29/64 (45%)	14/31 (45%)
Unfavorable IV (T4 and/or N3)	3/17 (18%)	7/43 (16%)

NED, no evidence of disease.
* 3000 cGy.
† 5500–7000 cGy.
(Parsons JT, Mendenhall WM, Million RR, Stringer SP, Cassisi NJ. The management of primary cancers of the oropharynx: combined treatment or irradiation alone? Semin Radiat Oncol 1992;2(3):144)

COMPLICATIONS OF TREATMENT: TONSILLAR AREA

The risk of bone and soft tissue complications for 136 patients treated initially by irradiation is outlined in Table 17-14.[23] Four patients (3%) required an operative procedure. The risk of severe complications with the 120-cGy twice-daily fractionation scheme was 3% for 97 patients; there were no moderate or severe complications for doses of 7440 to 7680 cGy, and the overall incidence of mild and moderate complications was reduced in comparison with results of once-a-day treatment (Parsons JT, unpublished study, March 1990).

The complications of combined treatment reported by Perez and associates are shown in Table 17-15.[32]

TREATMENT: SOFT PALATE

Selection of Treatment Modality

Small (2 to 5 mm), well-defined lesions may be excised, but the multifocal nature of soft palate lesions predicts marginal recurrence after limited treatment unless patients are carefully selected. Tiny lesions confined to the uvula may be treated by surgical excision with little morbidity. Irradiation is the modality most often selected for early and advanced soft palate carcinomas; neck dissection is added as needed. The success rate with irradiation is good, and it leaves the patient functionally intact without the need for a prosthesis or elaborate reconstruction.

TABLE 17-14. Tonsillar Area: Soft Tissue and/or Bone Complications by Severity (No. Complications/No. Treated)*

	Mild (1+)		Moderate (2+)		Severe (3+)	
T Stage	E†	E + R	E	E + R	E	E + R
T1	3/15 (20%)	No data	0/15	No data	0/15	No data
T2	10/41 (24%)	4/12 (33%)	2/41 (5%)	0/12	0/41	0/12
T3	4/23 (17%)	10/24 (42%)	1/23 (4%)	2/24 (8%)	4/23 (17%)	0/24
T4	2/14 (14%)	2/7	0/14	1/7	0/14	1/7

* 136 patients.

† E, external beam alone; E + R, external beam plus radium needle implant.

(Mendenhall WM, Parsons JT, Cassisi NJ, Million RR. Squamous cell carcinoma of the tonsillar area treated with radical irradiation. Radiother Oncol 1987;10:28)

Surgical Treatment

Lesions of the soft palate are approached transorally utilizing the Dingman mouth gag, which allows excellent exposure. Functional loss is minimal provided the resection is not completely through the thickness of the palate.

Surgical excision for early lesions (less than 5 mm) of the soft palate can achieve a high cure rate with little or no functional loss. Even through-and-through defects can be closed using local flaps, although velopharyngeal incompetence is also a potential hazard. If, however, a major resection is required, then a prosthesis is generally required to restore velopharyngeal competence. Surgical salvage of radiation recurrence should include full-thickness removal of the soft palate.

Irradiation Technique

The basic irradiation technique for early and advanced lesions involves parallel opposed external-beam portals that include the primary lesion and the upper neck nodes on both sides, since even patients with early lesions and a negative neck are at risk for lymph node metastasis (Fig. 17-17). If the primary lesion is discrete and technically suitable, a portion of the treatment may be given by intraoral cone or a single-plane implant. If intraoral cone therapy is to be used, it should be given before external-beam therapy when the lesion is clearly visible and the mouth is not yet sore (Fig. 17-18).

The dose for T1 and early T2 lesions is 6000 cGy over 6 weeks to 6400 cGy over 6½ weeks. If intraoral cone is used, treatment is initiated with 1500 to 2100 cGy (250 to 300 cGy per fraction) by intraoral cone followed by 4600 to 5000 cGy by external beam. The dose for larger lesions is usually 7000 cGy over 7 weeks or 120 cGy twice daily to 7440 to 7920 cGy; an implant may be added in selected cases.

If an implant is used, the external-beam dose is usually 5000 cGy over 5 weeks followed by 1500 to 3000 cGy by single-plane iridium-192 implant. We use the hairpin technique. The uvula may be difficult to include in the implant. Excision of the uvula at the time of the implant should be considered since it has been observed to be one of the sites of local failure after external-beam therapy or implant. The gutter guide technique can be done under general or local anesthesia with the patient in the sitting position. In either case, the palate is injected with local anesthetic to produce edema and facilitate placement of

TABLE 17-15. Carcinoma of the Tonsil: Complications of Treatment: A Comparison of Preoperative Irradiation Plus Surgery and Irradiation Alone

Complications of Preoperative Irradiation Plus Surgery	No. of Patients (n = 120)	Complications of Irradiation Alone	No. of Patients (n = 98)
Fatal	8 (7%)	Fatal	1 (1%)
Severe nonfatal		Severe nonfatal	
Pharyngocutaneous fistula	16 (13%)	Necrosis	6 (6%)
Severe dysphagia	8 (7%)	Severe dysphagia	5 (5%)
Carotid rupture (nonfatal)	2 (2%)	Other (hemorrhage, neuritis)	3 (3%)
Other severe (necrosis, wound breakdown, pneumonia)	14 (12%)		
Total	48 (40%)	Total	15 (15%)

(Modified from Perez CA, Purdy JA, Breaux SR, Ogura JH, von Essen S. Carcinoma of the tonsillar fossa: a nonrandomized comparison of preoperative radiation and surgery or irradiation alone: long-term results. Cancer 1982;50:2321)

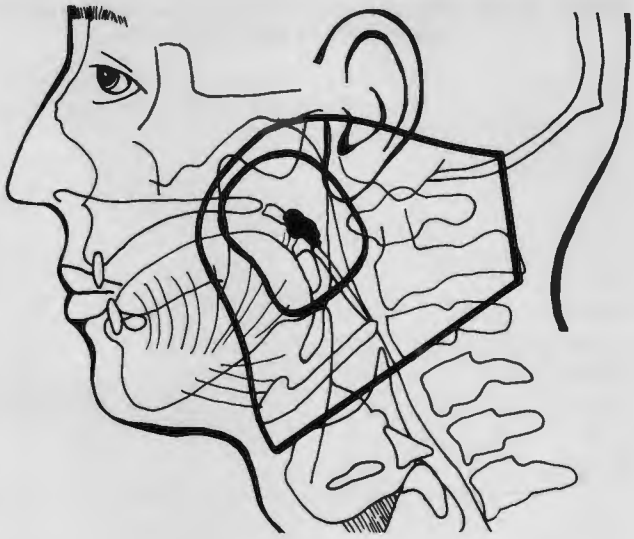
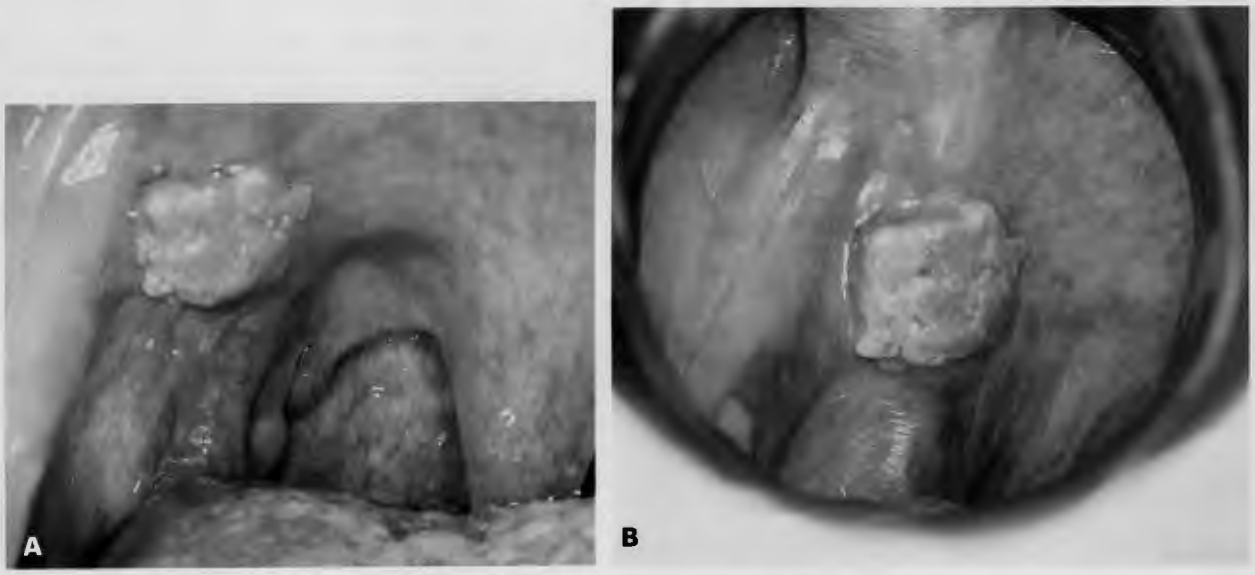


Figure 17-17. Initial and reduced lateral fields for treatment of carcinoma of the soft palate. The usual technique involves parallel opposed portals. The minimum treatment volume for early-stage disease includes the entire soft palate and the adjacent pillars. The timing and extent of field reductions after 5000 cGy depend on the status of the neck as well as the extent of the primary lesion. If the primary lesion extends to the midline or if clinically positive lymph nodes are present, both sides of the lower neck are irradiated. (Parsons JT, Million RR. Treatment of tumors of the oropharynx: radiation therapy. In: Thawley SE, Panje WR, eds. Comprehensive management of head and neck tumors, vol 1. Philadelphia, WB Saunders, 1987:694)



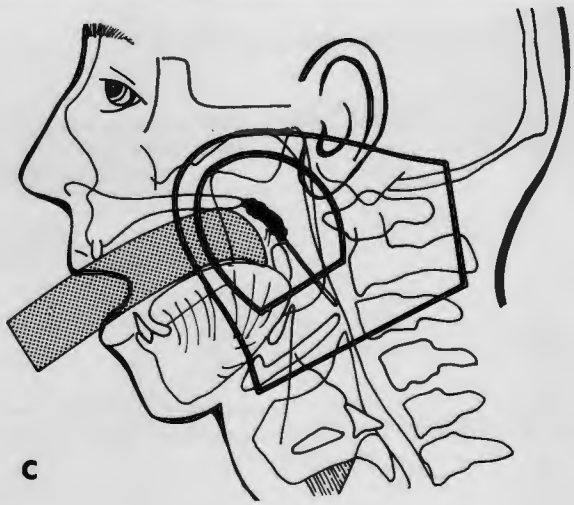


Figure 17-18. Intraoral cone treatment technique. (*A*) Exophytic invasive squamous cell carcinoma, 1.5 cm, of the right side of the soft palate. Discrete lesions in cooperative patients receive 1500 to 2000 cGy (250 to 300 cGy per fraction) with an intraoral cone before external beam irradiation. (*B*) View through intraoral cone shows adequate coverage of the lesion. (*C*) Treatment is completed by lateral portals that encompass the primary lesion and upper neck nodes plus a low neck portal. Use of an intraoral lead block reduces irradiation to the contralateral mucosa and parotid gland for well-lateralized lesions. (Parsons JT, Million RR. Treatment of tumors of the oropharynx: radiation therapy. In: Thawley SE, Panje WR, eds. Comprehensive management of head and neck tumors, vol 1. Philadelphia, WB Saunders, 1987:695)

TABLE 17-16. Carcinoma of Soft Palate and Uvula: Second Head and Neck Primary Cancers

Site	Synchronous	Metachronous	Total
Floor of mouth	4	3	7
True vocal cord	1	3	4
Oral tongue	1	2	3
Base of tongue	2	1	3
Pyriform sinus	1	1	2
Retromolar trigone	0	1	1
Alveolar ridge	0	1	1
Gingiva	1	0	1
Posterior pharyngeal wall	1	0	1
Posterior tonsillar pillar	1	0	1
Buccal mucosa	0	1	1

(Amdur RJ, Mendenhall WM, Parsons JT, Isaacs JH Jr, Million RR, Cassisi NJ. Carcinoma of the soft palate treated with irradiation: analysis of results and complications. Radiother Oncol 1987;9:190)

the gutter guides (see Fig. 14-20). One arm of the guide follows the free margin of the palate. Alternatively, single unlinked guides may be placed separately. Curved gutter guides may be fabricated to simulate the palate anatomy and simplify the implant. Plastic tube techniques are also described.[10] The implant may be done before external-beam therapy if the lesion is flat or after external-beam therapy if it is preferable to flatten the lesion before performing the implant.

The external-beam technique is usually equally weighted, parallel opposed portals. The minimum treatment volume for early lesions includes the entire soft palate, the adjacent tonsillar areas, and the upper neck nodes; the lower neck nodes are treated with a separate anterior low-neck portal. If the neck is clinically negative, high-energy photons (10 to 17 MV) will produce a tumor dose at the soft palate of 6500 to 7000 cGy and a minimum lymph node dose of 5000 cGy. If the lymph nodes are clinically positive, then cobalt-60 or 4 to 6 MV photons are preferred on the involved side. The entire neck on both sides is treated even for a clinically negative neck.

(For a time–dose analysis, see Fig. 12-9.)

Combined Treatment Policies

Combined therapy is rarely planned because of the success rate with radiation therapy and the morbidity associated with resection of the soft palate.

Management of Recurrence

Soft tissue necrosis is uncommon after radiation therapy, so a persistent ulcer is the hallmark of recurrent disease following irradiation. Recurrence following irradiation is treated by surgical removal when feasible, and salvage is achieved in a few patients. Frequent follow-up examination is important because of the high risk for second primary tumors of the head and neck, lung, and, esophagus (Table 17-16).[1]

RESULTS OF TREATMENT: SOFT PALATE

Surgical Results

Ratzer and coworkers reported the Memorial Sloan–Kettering results for 299 patients with squamous cell carcinoma of the soft palate.[35] One hundred twelve patients were treated by surgery, 139 by radiation therapy, and 22 by combined treatment. The 5-year absolute survival rate was 21%, and the cause-specific survival rate was 30%. The cause-specific survival rate for just the group treated by surgery was 38%. The main cause of failure was recurrence at the primary site.

Irradiation Results

Weller and associates reported a local control rate of 50% in 30 patients with soft palate lesions; only 5 had T1 lesions.[45]

Seydel and Scholl reviewed the results of 41 patients with previously untreated soft palate malignancies, including four nonsquamous carcinomas.[39] Thirty-one patients were treated with doses between 6000 and 7000 cGy, and 10(32%) developed local recurrence.

Amdur and associates reviewed the University of Florida results for 55 squamous cell carcinomas of the soft

TABLE 17-17. Soft Palate: Control of Disease at the Primary Site With Continuous-Course Irradiation*—55 Patients (No. Controlled/No. Treated)

T Stage	Excluded†	Initial Control	No. Salvaged/ No. Attempted	Ultimate Control
T1	2	8/8	No data	8/8
T2	7	14/19 (74%)	2/5	16/19 (84%)
T3	3	5/11 (45%)	0/2	5/11 (45%)
T4	1	1/4	No data	1/4

* Once-a-day or twice-a-day fractionation. Includes two patients who received most or all of their treatment with an interstitial implant.

† Patients were excluded from analysis of primary disease control if they died less than 2 years from treatment with no evidence of recurrence.

(Amdur RJ, Mendenhall WM, Parsons JT, Isaacs JH Jr, Million RR, Cassisi NJ. Carcinoma of the soft palate treated with irradiation: analysis of results and complications. Radiother Oncol 1987;9:187)

TABLE 17-18. Soft Palate: Control of Disease Above the Clavicles Using Continuous-Course Irradiation—55 Patients (No. Controlled/ No. Treated)

Modified AJCC Stage	Excluded*	Initial Control	No. Salvaged/ No. Attempted	Ultimate Control
I	1	7/8	1/1	8/8
II	2	9/13 (69%)	2/3	11/13 (85%)
III	1	5/10	2/4	7/10
IVA	2	0/2	0/1	0/2
IVB	5	4/11 (36%)	0/2	4/11 (36%)

* Patients were excluded from analysis of control of disease above the clavicles if they died less than 2 years from treatment with no evidence of recurrence at that particular site.
(Amdur RJ, Mendenhall WM, Parsons JT, Isaacs JH Jr, Million RR, Cassisi NJ. Carcinoma of the soft palate treated with irradiation: analysis of results and complications. Radiother Oncol 1987;9:189)

palate treated by continuous-course radiation therapy from 1964 to 1983. The local control rates by T stage are shown in Table 17-17, and the ultimate control rates by stage are shown in Table 17-18.[1] The current rate of local control for patients treated by twice-daily fractionation is 8 of 8 for T2 and 5 of 9 for T3 (Parsons JT, unpublished study, March 1991).

The 2- and 5-year survival rates are shown in Table 17-19. The 5-year cause-specific survival rate is lower than for patients with base of tongue or tonsillar region tumors of similar stages. The results from published articles are summarized in Table 17-20.

COMPLICATIONS OF TREATMENT: SOFT PALATE

Surgical Complications

Nasal speech and regurgitation of liquids or solids into the nasopharynx are sequelae of full-thickness resection of the soft palate. A prosthesis is not always completely successful in correcting the functional defect.

Complications of Irradiation

Varying degrees of xerostomia occur in most patients. Persistent soft tissue necrosis of the soft palate is uncommon. The soft palate may become retracted following successful treatment of advanced lesions, and this may result in regurgitation into the nasopharynx and slight alteration in speech. Small perforations may persist after successful treatment at sites where tumor has grown through the soft palate. Trismus may occur in advanced cases. Otitis media is an infrequent side effect. Complications reported by the University of Florida are outlined in Table 17-21. One patient with a T3 lesion required mandibulectomy for osteoradionecrosis.

There have been no severe complications for 20 patients with T2 to T4 lesions treated by the twice-a-day fractionation scheme (Parsons JT, unpublished study, March 1991).

TABLE 17-19. Soft Palate: Survival Using Continuous-Course Irradiation (No. Alive/No. Treated)

Modified AJCC Stage	No. of Patients	2-Year		5-Year	
		Absolute	Cause-Specific	Absolute	Cause-Specific
I	8	7/8	7/8	5/8	5/6
II	15	13/15 (87%)	13/13 (100%)	7/13 (54%)	7/9
III	12	10/12 (83%)	10/12 (83%)	3/10	3/8
IVA	4	1/4	1/2	0/4	0/2
IVB	16	4/16 (25%)	4/10	2/15 (13%)	2/8

(Amdur RJ, Mendenhall WM, Parsons JT, Isaacs JH Jr, Million RR, Cassisi NJ. Carcinoma of the soft palate treated with irradiation: Analysis of results and complications. Radiother Oncol 1987;9:190)

TABLE 17-20. Literature Review for Squamous Cell Carcinoma of the Soft Palate

Series	No. of Patients (Follow-up)	Primary Treatment	Staging System	Ultimate Control of Disease at Primary Site*	5-Year Cause-Specific Survival†
Amdur et al University of Florida, 1987[1]	55 (≥2 y)	RT alone	AJCC	T1, 100%; T2, 84%; T3, 45%; T4, 1/4	I, 83%; II, 78%; III, 38%; IV, 20%
Chung and Constable University of Virginia, 1979[6]	63 (≥2 y)	Individualized; RT alone in 51%	AJCC	T1, 100%; T2, 83%; T3, 52%; T4, 2/5	T1–2, 70%; T3–4, 25%
Lindberg and Fletcher M.D. Anderson Hospital, 1978[21]	(NS) (≥2 y)	Individualized; RT alone in 70%	AJCC	T1, 100%; T2, 100%; T3, 82%; T4, 83%	NS
Garrett and Beale Princess Margaret Hospital, 1984[14]	70 (≥2 y)	RT alone	UICC	T1, 90%; T2, 95%; T3, 56%	T1, 65%; T2, 84%; T3, 28%
Seydel and Scholl Fox-Chase Center, Philadelphia, 1974[39]	41 (NS)	Individualized; RT alone in 73%	AJCC	T1, 83%; T2, 87%; T3, 46%; T4, no data‡	Overall 54%
Eneroth et al Karolinska Institute, 1972[9]	112§ (≥5 yrs)	Individualized	NS	Overall 86%	Overall 37%
Weller et al Stanford, 1976[45]	30 (≥2 y)	RT alone	UICC	Overall 50%	Overall 38%#
Fee et al Stanford and UC(SF), 1979[11]	106 (NS)	Individualized; RT alone in 75%	AJCC	NS	I, 75%; II, 29%; III, 30%; IV, 18%
Ratzer et al Memorial Sloan–Kettering, 1970[35]	299¶ (≥5 y)	Individualized; RT alone in 39%	NS	NS	Overall 30%**

NS, not specified; AJCC, American Joint Committee on Cancer; UICC, International Union Against Cancer.
* Includes the results of salvage therapy.
† Excludes deaths from intercurrent disease.
‡ Control with initial treatment, not ultimate control results. Two additional patients were successfully salvaged with surgery.
§ Includes lesions of hard as well as soft palate.
# Absolute, not determinate survival figure.
¶ 18% of patients had recurrent lesions following prior treatment at another institution.
** Disease-free survival figure.
(Amdur RJ, Mendenhall WM, Parsons JT, Isaacs JH Jr, Million RR, Cassisi NJ. Carcinoma of the soft palate treated with irradiation: analysis of results and complications. Radiother Oncol 1987;9:193)

TABLE 17-21. Soft Palate: Soft Tissue and/or Bone Complications by Severity With Continuous-Course Irradiation (No. Complications/No. Treated)

T stage	No. Patients	Mild (1+)	Moderate (2+)	Severe (3+)
T1	10	1	0	0
T2	26	2	0	0
T3	14	0	1	1
T4	5	2	0	0

(Amdur RJ, Mendenhall WM, Parsons JT, Isaacs JH Jr, Million RR, Cassisi NJ. Carcinoma of the soft palate treated with irradiation: analysis of results and complications. Radiother Oncol 1987;9:189)

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18

LARYNX

RODNEY R. MILLION, NICHOLAS J. CASSISI, AND ANTHONY A. MANCUSO

Cancer of the larynx represents about 2% of the total cancer risk and is the most common head and neck cancer (skin excluded). The number of new cases in 1993 in the United States is estimated at 12,600 (10,000 in men and 2,600 in women) with an estimated 3,800 deaths due to laryngeal cancer.[9] Localized cases are estimated at 65%, those with regional spread around 30%, and those with distant metastasis at the time of first diagnosis at 5%. The ratio of glottic to supraglottic carcinoma is about 3 : 1.

A study of trends in cancer incidence in the United States from 1935 to 1970 shows that cancer of the larynx has increased by 33% in white men but is three and one-half times greater in nonwhite men. The incidence in women has shown only a minimal increase, in spite of the fact that lung cancer in women has quadrupled in the same period.[14]

Cancer of the larynx seems to be primarily related to cigarette smoking. Marijuana is suspected as a causative agent. The risk of tobacco-related cancers of the upper alimentary and respiratory tract declines among ex-smokers after 5 years and is said to approach the risk of nonsmokers after 10 years of abstention.[89]

A 12-year American Cancer Society study has shown that smoking low-tar and low-nicotine cigarettes (less than 18 mg of tar and less than 1.2 mg of nicotine) results in slightly lower death rates from lung cancer, but whether the risk of laryngeal cancer is affected is unknown.[27] The importance of alcohol in the etiology of laryngeal cancer remains unclear, but it is probably less important than in cancer in other head and neck sites.[82]

The geographic distribution for laryngeal cancer in the United States shows excess occurrence in the Northeast, particularly in northern New Jersey, New York City, and along the Hudson River. The rates are also high along the southeastern Atlantic coast and the Gulf coast. This distribution closely resembles the high-risk areas for lung cancer.[20]

ANATOMY

The anatomy of the larynx has been studied in great detail in recent years by whole-organ serial sections. These studies provide the basis for understanding not only the anatomy but also the routes of local tumor spread and the basis for partial laryngectomies, both the vertical hemilaryngectomy and the horizontal supraglottic laryngectomy. Anatomically, the larynx is divided into the supraglottic, glottic, and subglottic regions. The supraglottic larynx consists of the epiglottis, the false vocal cords, the ventricles, and the aryepiglottic folds, including the arytenoids. The glottis includes the true vocal cords and the anterior commissure. The subglottic area is located below the vocal cords (Figs. 18-1 and 18-2 and Color Figs. 10 through 12).[12,53]

The line of demarcation between the glottis and the supraglottic larynx is considered from the clinical viewpoint to be the point at which the epithelium of the vocal cord turns upward to form the lateral wall of the ventricle. The demarcation between the glottis and subglottis is also ill defined but is considered to begin 5 mm below the free margin of the vocal cord and to end at the inferior border of the cricoid cartilage. The subglottic area is about 1.5 cm in length in the adult male.

The vocal cords are about 2.2 cm in length in men and 1.8 cm in women. They are 3 to 5 mm thick, being relatively thin at the anterior commissure, thicker in their midportion, and then slightly thinner at the vocal process. Technically, the vocal cords terminate posteriorly with their attachment to the vocal process. The mucosa between the arytenoids forms the posterior part of the glottis (ie, the posterior commissure).

Framework

The framework of the larynx is composed of bone and cartilage joined together by numerous ligaments. The outside shell is formed by the hyoid bone, thyroid carti-

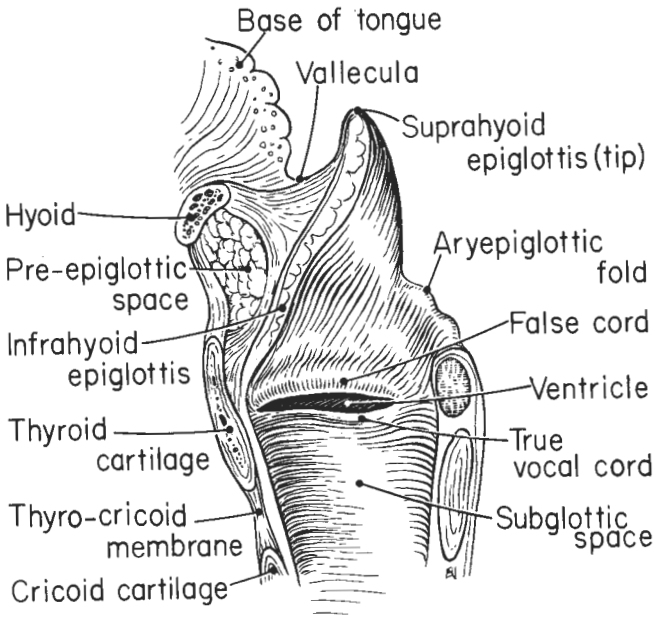


Figure 18-1. Diagrammatic sagittal section of the larynx. (Redrawn from Sobotta drawings. In: Clemente CD: Anatomy: a regional atlas of the human body, ed 3. Munich, Urban & Schwarzenberg, 1987)

lage, and cricoid cartilage, with the cricoid cartilage being the only complete ring. The more mobile interior framework is composed of the heart-shaped epiglottis and the arytenoid, corniculate, and cuneiform cartilages. The corniculate and cuneiform cartilages produce small, rounded bulges at the posterior end of the aryepiglottic folds.

Adult cartilage has no blood vessels and no lymphatics and is mostly an interstitial substance with few cells of low mitotic activity. The thyroid, the cricoid, and a portion of the arytenoids are hyaline cartilage and become calcified and then ossified with age, particularly in men, and develop a blood supply and a marrow cavity. The thyroid and cricoid cartilages tend to develop cortical calcification with an intervening medullary space containing fat at times admixed with residual islands of cartilage at various stages of calcification. Ossification, when it occurs, is patchy and makes interpretation of computed tomography (CT) and magnetic resonance imaging (MRI), as well as standard roentgenograms, difficult when evidence of framework invasion is sought. The remaining cartilages are of the elastic variety and do not ossify, although small areas of calcification are occasionally seen on CT scans.

The epiglottic cartilage and thyroepiglottic ligament are porous, especially the infrahyoid portion, owing to the multiple foramina for the ducts of minor salivary glands (see Color Figs. 10*A* and 12).

The hyoid bone and various cartilages are joined together by an elaborate system of ligaments and fibroelastic membranes, including the thyrohyoid, cricothyroid, and the cricotracheal ligaments or membranes (Fig. 18-3). All three of these ligaments are thin, and the thyrohyoid in particular is rather flimsy and a poor barrier to tumor spread. There is a small gap between the middle and inferior pharyngeal constrictor muscles where the neurovascular bundle penetrates the thyrohyoid membrane; this weak point allows ready exit into the neck for tumors involving the lateral pharyngeal wall (see Chap. 20).

The epiglottis is joined superiorly to the hyoid bone by the hyoepiglottic ligament. The epiglottis is joined to the thyroid cartilage by the thyroepiglottic ligament at a point just below the thyroid notch and above the anterior commissure (see Color Fig. 12). The arrangement of the ligaments that connect the cricoid and arytenoid cartilages and form the vocal ligaments, which are part of the true vocal cords, is shown in Figure 18-2*D*. The conus elasticus (cricovocal ligament) is the lower portion of the elastic membrane that joins the upper surface of the cricoid, the vocal process of the arytenoid, and the lower thyroid cartilage; its upper free border is thickened into the vocal ligament. Each arytenoid cartilage rests on top of the cricoid cartilage; the cricoarytenoid joint is lined by a synovial membrane (see Color Fig. 11). The vocal ligaments and muscles attach to the vocal process of the arytenoid posteriorly and the thyroid cartilage anteriorly.

The two true vocal cords meet anteriorly to form the anterior commissure tendon, which inserts into the thyroid cartilage.

Muscles

The arrangement of the intrinsic muscles of the larynx, which primarily control the movement of the cords, is presented in Figure 18-2*B* and Color Figs. 10 through 12. The extrinsic muscles are concerned primarily with swallowing, except for the cricothyroid muscle, which produces tension and elongation of the vocal cords and is innervated by the superior laryngeal nerve (see Figs. 18-3 and 18-4).

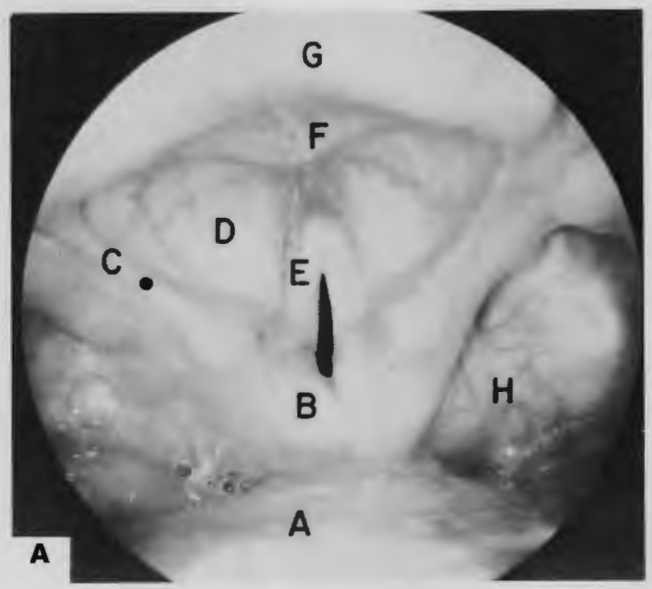
Fat Spaces

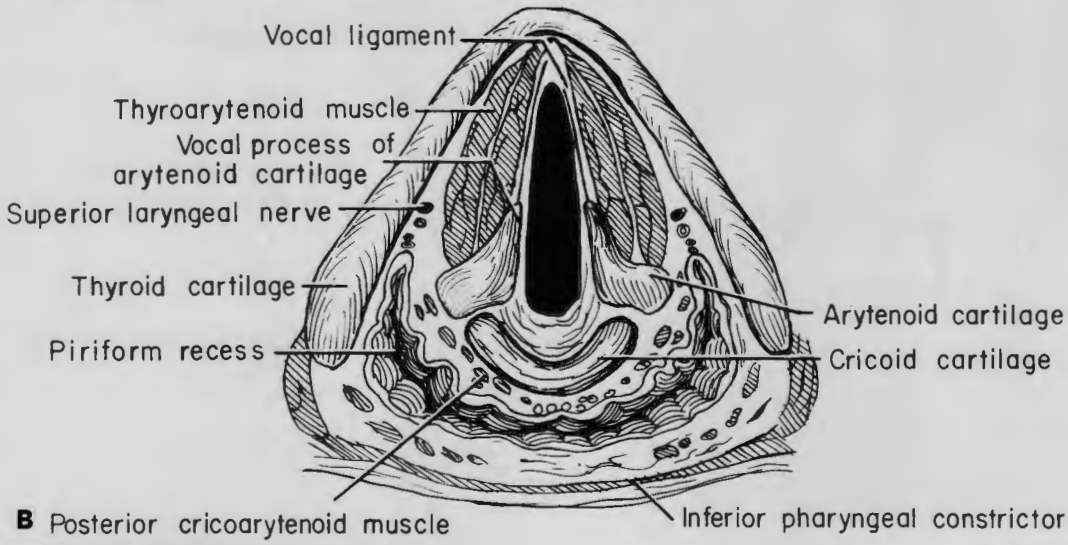
The preepiglottic and paraglottic fat spaces are essentially one continuous space lying between the external framework of the thyroid cartilage and hyoid bone and the inner framework of the epiglottis and intrinsic muscles (see Color Figs. 10 through 12). This fatty areolar space is traversed by blood and lymphatic vessels and nerves; there should be few, if any, capillary lymphatics arising in this area, and therefore invasion of the fat space should only indirectly be associated with lymph node metastases. The fat space is limited by the conus elasticus inferiorly; the thyroid ala, thyrohyoid membrane, and hyoid bone anterolaterally; the hyoepiglottic ligament superiorly; and the fascia of the intrinsic muscles on the medial side. Posteriorly it is in relationship to the anterior wall of the pyriform sinus. The fat space is thus semilunar or horseshoe-shaped on cross section and is easily seen on CT and MRI studies because of the good contrast of fat with surrounding tissues (see Fig. 18-2*C*).

Mucous Membrane

The laryngeal surface of the epiglottis and the free margin of the vocal cords are squamous epithelium, and the remainder is usually pseudostratified ciliated columnar epithelium. The stratified squamous epithelium of the vocal cord extends on the average 1.8 mm lateral and 2.3

(*text continues on page 438*)





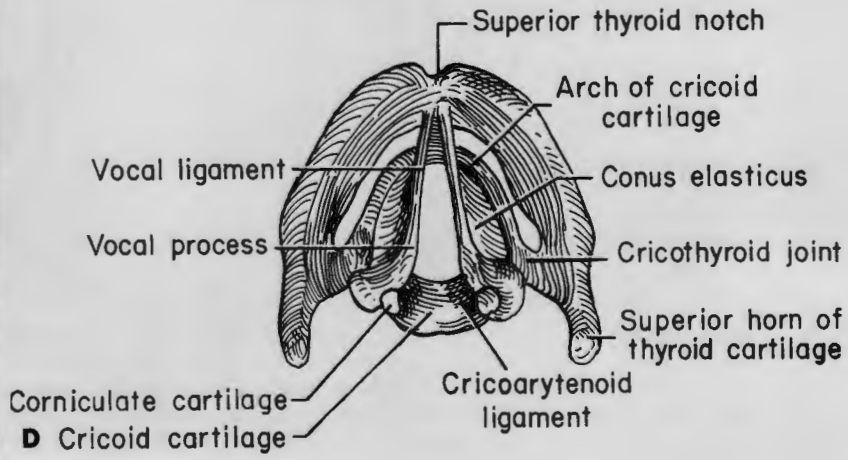
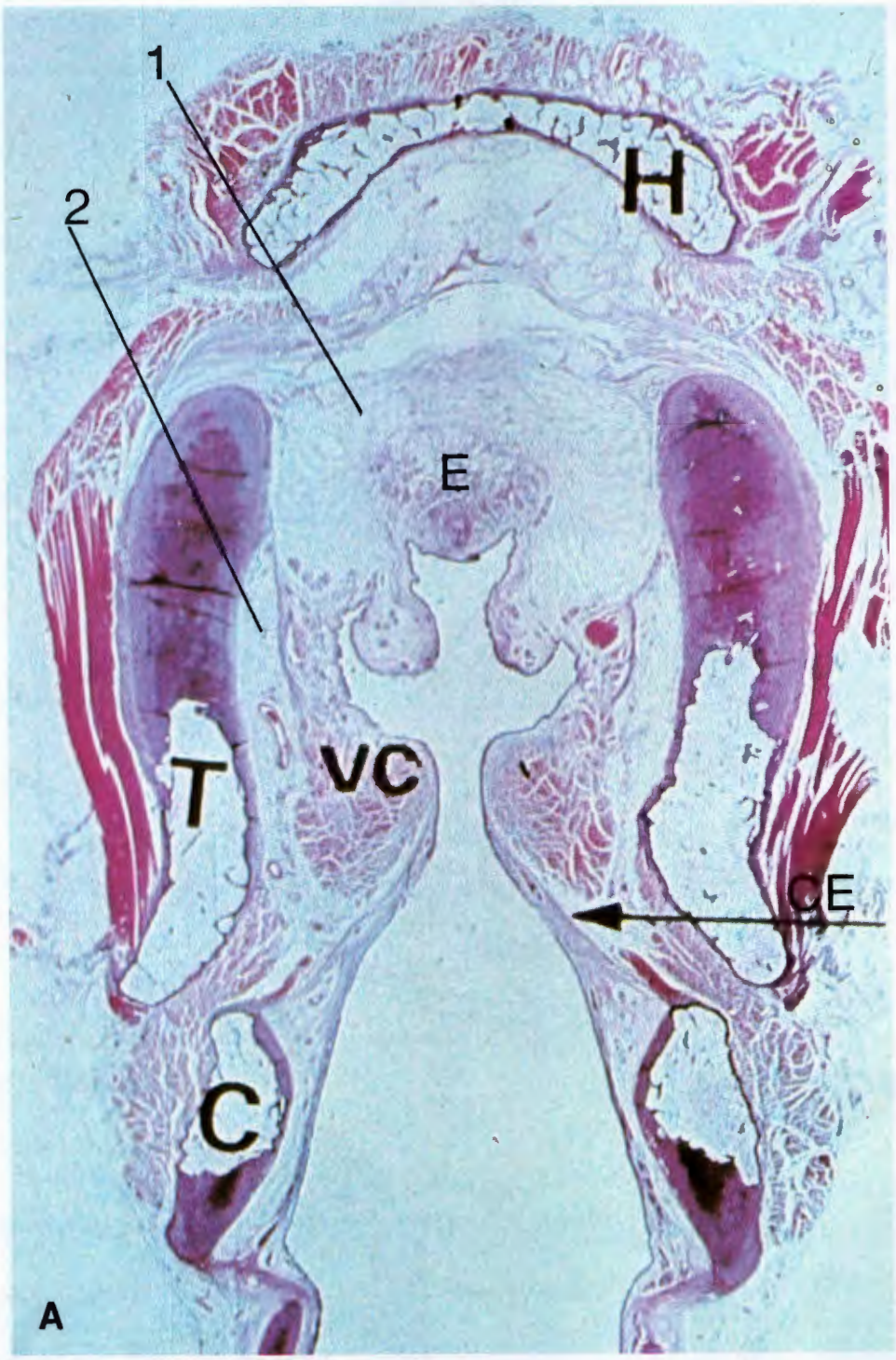
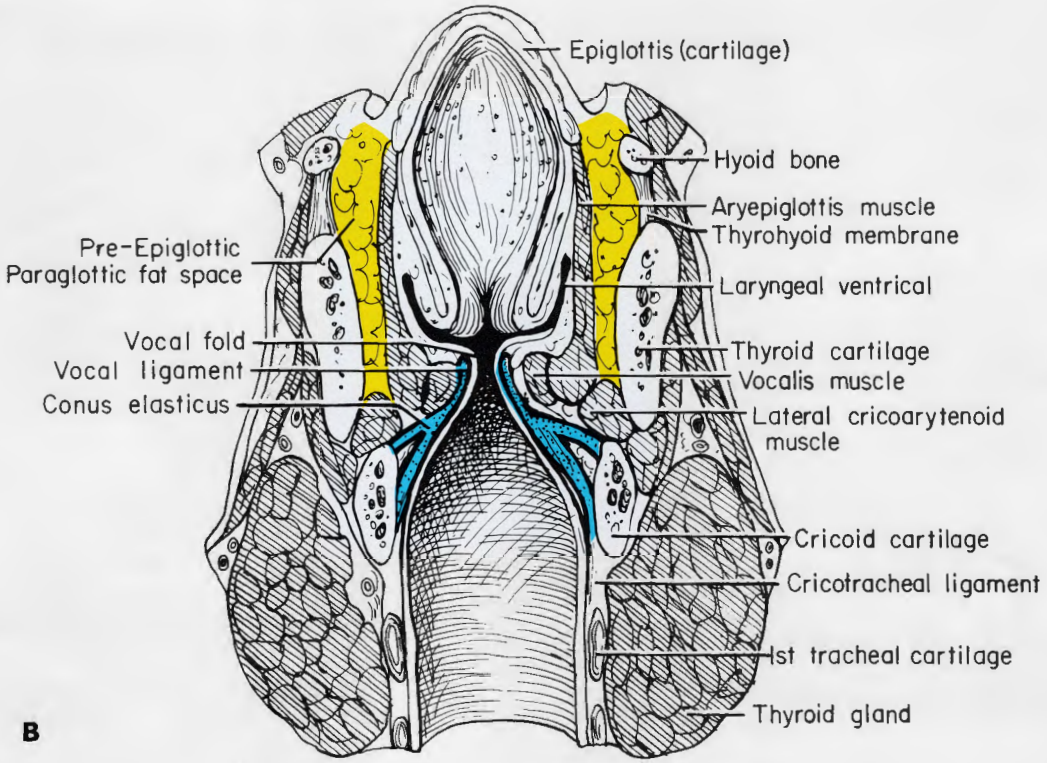
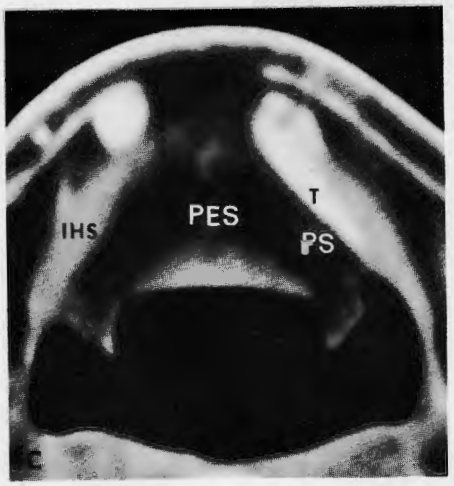


Figure 18-2. (*A*) Larynx. A, posterior pharyngeal wall; B, arytenoid; C, aryepiglottic fold; D, false vocal cord; E, true vocal cord; F, infrahyoid epiglottis; G, suprahyoid epiglottis; H, pyriform sinus. (*B*) Cross-section of larynx at level of vocal cords. (*C*) CT scan at the level of the vocal cords. Note the thin low-density paraglottic space between the lateral margins of the vocal cords and the thyroid cartilage (*arrow*). The top of the cricoid cartilage (C) and the arytenoid cartilages (A) are also visible at this level. Note the vocal process of the arytenoid (*arrowhead*). (*D*) Framework of the larynx. (*A* from Million RR, Cassisi NJ. Malignant tumors of the larynx. In: Carter SK, Glatstein E, Livingston RB eds. Principles of cancer treatment, New York, McGraw-Hill, 1982:635; *B* and *D* redrawn from Sobotta drawings. In: Clemente CD: Anatomy: a regional atlas of the human body, ed 3. Munich, Urban & Schwarzenberg, 1987)

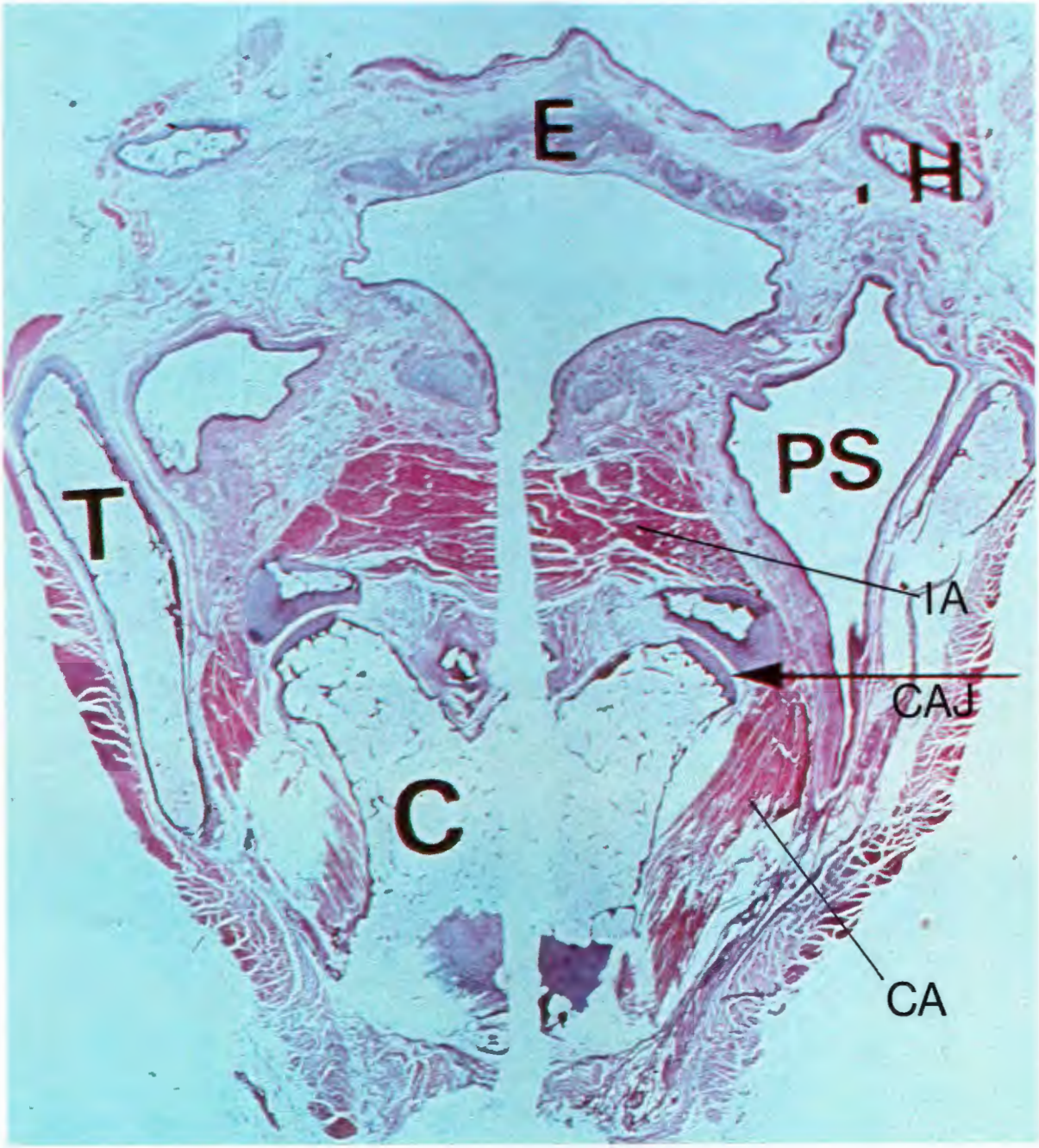


Color Figure 10. (*A*) Coronal whole-organ laryngeal section near middle third of vocal cord. The conus elasticus (CE) extends from the cricoid cartilage (C) to the vocal cord (VC). The thyroid cartilage (T) is partially ossified as is the cricoid cartilage; a CT scan might be interpreted as "cartilage destruction" when, in fact, there is a normal partially ossified cartilage. The epiglottis (E) is seen surrounded by the preepiglottic (1) and paraglottic (2) fat spaces, which extend inferiorly to the conus elasticus (H, hyoid bone). (*B*) Coronal diagram of larynx. (*C*) Axial CT sections through the mid supraglottic larynx. The section just skims the upper margin of the thryoid cartilage on the left (T); note that only the infrahyoid strap muscles (IHS) are visible on the right side. The preepiglottic space (PES) is broadly continuous with the adjacent paraglottic spaces (PS). (*A*, courtesy of A. W. P. van Nostrand, Toronto General Hospital, Ontario, Canada; *B*, redrawn from Sobotta drawings. In: Clemente CD: Anatomy: a regional atlas of the human body, ed 3. Munich, Urban & Schwarzenberg, 1987)

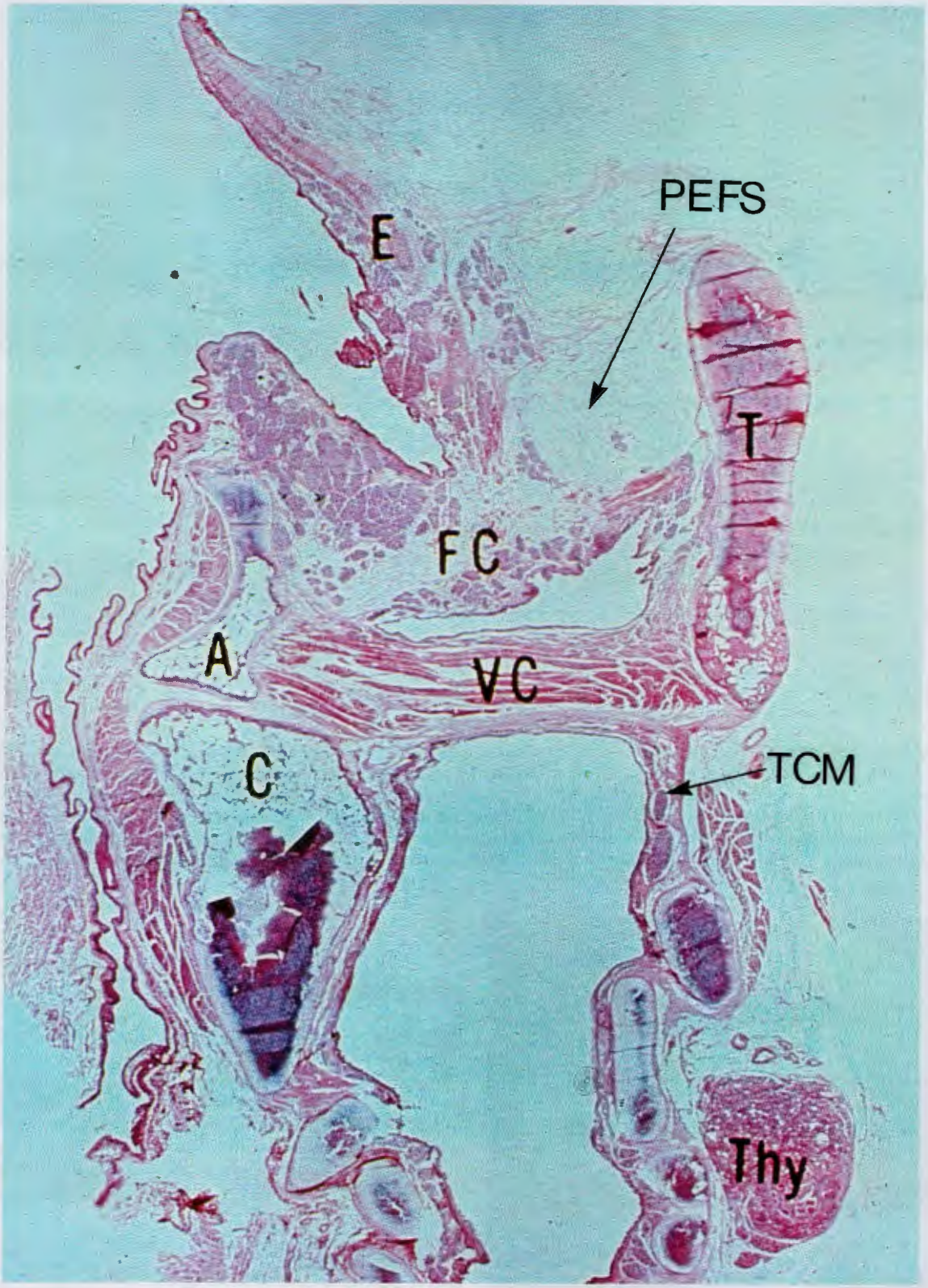




Color Figure 10. (*Continued*)



Color Figure 11. Whole-organ laryngeal coronal section of normal larynx through the posterior aspect of cricoid cartilage. The thyroid (T) and cricoid (C) cartilages are composed almost entirely of marrow-containing bone. The arrow points to the cricoarytenoid joint (CAJ); note proximity to the lower medial wall of the pyriform sinus (PS). The distance between the mucosa of the lateral wall of the pyriform sinus and the cartilage is narrow. The thyrohyoid and thyrocricoid membranes are indistinct. Fixation of the vocal cord may occur when tumor invades the cricoarytenoid joint, the cricoarytenoid muscle (CA), or the interarytenoid muscle (IA). E, epiglottis; H, hyoid bone. (Courtesy of A. W. P. van Nostrand, Toronto General Hospital, Ontario, Canada)



Color Figure 12. Whole-organ sagittal section of normal larynx just to the left of the midline. The lower portion of the epiglottic (E) cartilage is perforated by the ducts of numerous minor salivary glands and appears discontinuous. The preepiglottic fat space (PEFS) is clearly seen. The ventricle lies between the false cord (FC) and the vocal cord (VC). The arytenoid (A) and cricoid cartilage (C) are ossified. The thyrocricoid membrane (TCM) can be identified. There is no obvious anatomical barrier to the spread of supraglottic lesions to the vocal cord or vice versa. Thy, thyroid; T, thyroid cartilage. (Courtesy of A. W. P. van Nostrand, Toronto General Hospital, Ontario, Canada)

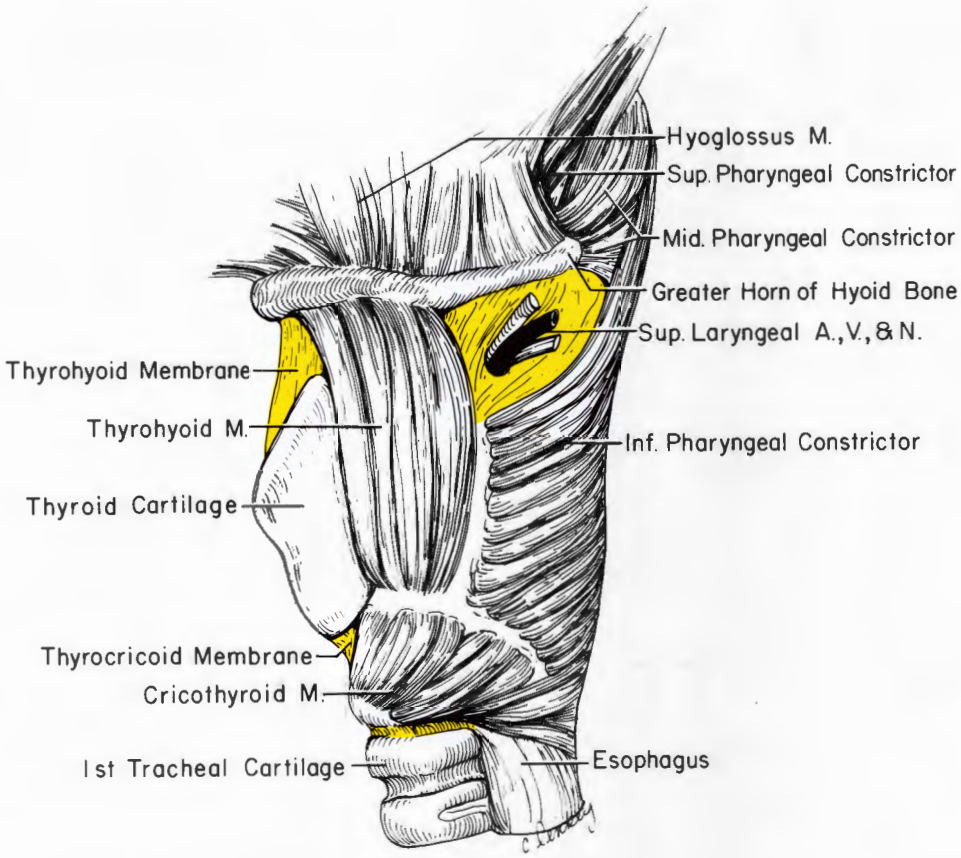


Figure 18-3. External view of the larynx. (Redrawn from Sobotta drawings. In: Clemente CD: Anatomy: a regional atlas of the human body, ed 3. Munich, Urban & Schwarzenberg, 1987)

mm inferior to the free edge of the vocal cord. Beneath the epithelium of the free edge of the vocal cord is the lamina propria, which can be divided into three layers.

The outer layer (0.3 mm thick) is loosely organized elastic and collagenous fibers with physical characteristics similar to soft gelatin; this layer is referred to as Reinke's space, the space where edema develops. The intermediate and deep layers of the lamina propria (0.8 mm thick) are composed of densely organized elastic and collagenous fibers, and these two layers are referred to as the vocal ligament. Fibers of the vocal ligament insert into the underlying vocalis muscle so that there is no sharp distinct border.

There is no true submucosal layer along the free margin of the vocal fold.[34]

Figure 18-4. Bilateral superior laryngeal nerve paralysis results in "bowing" of the vocal cords.

Blood Supply

The laryngeal arteries are branches of the superior and inferior thyroid arteries. The super laryngeal artery, as part of the neurovascular bundle, enters the larynx laterally through the thyrohyoid membrane at the junction of the middle and inferior constrictor muscles. The inferior laryngeal neurovascular bundle penetrates the cricopharyngeal muscle, just posterior to the cricothyroid joint, to enter the larynx.

Nerve Supply

The intrinsic muscles of the larynx are innervated by the recurrent laryngeal nerve. The cricothyroid muscle, an extrinsic muscle responsible for tensing the vocal cords, is supplied by a branch of the superior laryngeal nerve; isolated damage to this nerve causes a "bowing" of the true vocal cord (see Fig. 18-4). The vocal cord continues to be mobile, but the voice may become hoarse. Loss of

the sensory function of one superior laryngeal nerve (the "watchdog of the larynx") does not usually produce problems. The endolaryngeal nerve of Galen connects the recurrent laryngeal and superior laryngeal nerves.

Lymphatics

The supraglottic structures have a rich capillary lymphatic plexus. The lymphatic collecting trunks pass through the preepiglottic space and the thyrohyoid membrane and terminate mainly into the subdigastric lymph nodes; a few trunks drain directly to the middle internal jugular chain lymph nodes.

The true vocal cords have essentially no capillary lymphatics; as a result, lymphatic spread from glottic cancer occurs only when tumor extends to supraglottic or subglottic areas, and even then the risk of lymph node metastases for T2 glottic lesions is small. The subglottic area has relatively few capillary lymphatics. The lymphatic trunks pass through the cricothyroid membrane to the pretracheal (Delphian) lymph node(s), or the trunks may connect to the lower internal jugular lymph nodes and the lateral paratracheal lymph nodes (see Chap. 6). The pretracheal nodes are midline in position and even when clinically positive are small (1 to 5 mm and rarely over 1 to 2 cm). The subglottic area also drains posteriorly through the cricotracheal membrane, with some trunks going to the lateral paratracheal lymph nodes while others pass to the inferior jugular chain. The lateral paratracheal lymph nodes are continuous with lymph nodes in the upper mediastinum.

PATHOLOGY

The laryngeal surfaces of the epiglottis and vocal cords are lined with stratified squamous epithelium, and the remainder of the larynx is lined with pseudostratified ciliated columnar epithelium. Nearly all malignant tumors of the larynx arise from the surface epithelium and therefore are squamous cell carcinoma or one of its variants. Metastases to the larynx, usually the supraglottic area, are reported.

Carcinoma in situ occurs frequently on the vocal cords. Distinction between dysplasia, carcinoma in situ, squamous cell carcinoma with microinvasion, and true invasive carcinoma is a problem that the pathologist and the clinician frequently confront. Stripping of the entire membranous cord in patients with minimal lesions serves as the biopsy of the mucosa; the specimen tends to curl or fold, creating difficulty in orientation of the basement membrane. Most of the vocal cord carcinomas are either well differentiated or moderately well differentiated. In a few cases there is an apparent carcinoma and sarcoma occurring together, but almost all of these are in reality a squamous carcinoma with pseudosarcomatous or spindle cell stromal reaction. Some of the spindle cell carcinomas present in the larynx and trachea as a polypoid or pedunculated tumor with a stringlike umbilical cord; they have a favorable prognosis.

Verrucous carcinoma is reported to occur in 1% to 2% of patients with carcinoma of the vocal cord. The histologic diagnosis is difficult and must correlate with the gross appearance of the lesion.

Supraglottic carcinomas are less differentiated than those of the vocal cord, and verrucous lesions are rare. Carcinoma in situ is rarely diagnosed as a distinct entity in the supraglottic larynx, although a zone of carcinoma in situ may be seen at the margin between invasive tumor and normal mucosa.

Small cell carcinoma ("oat cell") is rarely diagnosed in the supraglottic larynx and should be recognized as such because of its biologic potential for rapid growth, early dissemination, and responsiveness to chemotherapy and irradiation.

Minor salivary gland tumors, usually adenoid cystic carcinoma, arise from the mucous glands in the supraglottic and subglottic larynx, but they are rare. Even more rare is the appearance of a chemodectoma, carcinoid, soft tissue sarcoma, malignant lymphoma, or plasmacytoma. (See the appropriate chapters for further discussion.) Benign chondromas and osteochondromas are reported; their malignant counterparts are rare.

PATTERNS OF SPREAD

Local Spread

The patterns of spread for squamous cell carcinoma are governed by the normal anatomic barriers and whether the lesion is infiltrative or develops with pushing borders. In explaining spread patterns, much has been made of the fact that the supraglottic larynx and the glottic/subglottic areas develop from different embryonic origins. Although there is a tendency for supraglottic and glottic lesions to remain confined to their original compartments, there is no anatomic barrier to growth from one area to the next. Glottic lesions tend to be slow growing, but eventually they extend to the supraglottic and subglottic areas. Supraglottic lesions do not often start near the vocal cords, so that involvement of the cords on their external epithelial surface is usually a late phenomenon; submucosal extension to the vocal cords by way of the paraglottic space may occur. The fibrous tissue at the anterior commissure is a relative barrier to submucosal tumor spread from the epiglottis to the anterior commissure of the vocal cord; spread to the anterior commissure at this point is mainly on the surface.[4]

The predominantly fatty preepiglottic and paraglottic spaces are important avenues of submucosal tumor spread for infrahyoid epiglottis, false cord, and true vocal cord lesions (see Color Figs. 10 through 12). As the false cord and true vocal cord lesions penetrate laterally, they quickly encounter the thyroid cartilage and then grow along the paraglottic space and even through the cricothyroid membrane before invading the perichondrium and cartilage. As the tumor grows inferiorly within the paraglottic space, it is shunted by the conus elasticus, at first toward and eventually through the cricothyroid membrane and into the tissues of the neck and the thyroid gland. Extralaryngeal spread is most often contained by the infrahyoid strap muscles but in advanced cases may go on to breach the fascia and directly invade the deep neck soft tissues.

When thyroid cartilage invasion occurs, it is usually in an ossified section of the cartilage. The posterior portions of the thyroid and cricoid cartilages are more commonly ossified, but invasion is most often observed at the anterior commissure, inferior borders of the thyroid cartilage, and the upper border of the cricoid since glottic cancers most commonly arise in this region. The point of invasion of the ossified cartilage is probably at the sites

of small fissures created by penetrating ligaments and connecting membranes. Cancers spreading inferiorly along the conus elasticus and cricothyroid membrane will invade the upper margin of the cricoid and lower margin of the thyroid cartilage. Supraglottic cancers infrequently invade the thyroid cartilage, but when this occurs it is usually at the insertion of the thyrohyoid membrane on the upper surface of the thyroid cartilage especially near the thyroid notch. Even though tumor spreading in the paraglottic space may have a broad interface with the perichondrium of the thyroid cartilage, direct invasion of the medial aspect of the cartilage, away from its edges and sites of membranous and musculotendinous insertions, occurs relatively infrequently. Such invasion may be along vessels penetrating the ossified cartilage.

Micheau and coworkers studied 120 cases of T2 to T4 laryngeal cancer in patients without prior irradiation.[51] Partial or total ossification of the thyroid and cricoid cartilages occurred in 93%. Tumor invasion of cartilage was found in 70 patients, and in 66 the invasion occurred in the ossified portion. The most common site of thyroid cartilage invasion occurs at the anterior angle. Micheau and coworkers reported three unusual cases in which the internal portion of the cartilage was totally replaced by tumor, which expanded the cartilage, giving it a "blown up" or expanded appearance. Isolated satellite nodules were reported in 18 of the 120 cases; in six instances, the satellites were distal.[51]

Archer and associates of St. Louis University have correlated CT findings with the incidence of cartilage/bone invasion on whole-organ sections.[3] CT scans were made at 2-mm intervals. Whole-organ sections were made at 4-mm intervals parallel to the CT sections. The maximum dimension of the tumor mass was measured in two directions and divided by two to give an average maximum diameter. When the average diameter of the tumor mass was greater than 16 mm and the lesion was located below the top (apex) of the arytenoid, 12 of 14 patients had cartilage invasion on pathologic examination. Nine of the 12 had three cartilages invaded. Cartilage invasion could only be detected by microscopic examination in eight. Lesions whose maximum diameter lay above the arytenoid showed a low risk (1 of 12) for invasion of the thyroid, cricoid, and arytenoid cartilages. There was no comment regarding invasion of the epiglottic cartilage.

Kurita and associates studied whole-organ sections in 51 laryngectomy specimens. The incidence of thyroid and cricoid cartilage invasion according to T stage is shown in Tables 18-1 and 18-2. Invasion occurred at the anterior commissure, the lower border of the thyroid cartilage, or the upper border of the cricoid.[39]

TABLE 18-1. Incidence of Thyroid Cartilage Invasion on Whole-Organ Laryngectomy Sections

	T1	T2	T3	T4
Supraglottic	0/1	1/8	1/10	0/2
Glottic	1/2	4/8	8/16	1/1
Subglottic	No data	1/1	0/1	1/1

(Adapted from Kurita S, Hirano M, Matsuoka H, Tateishi M, Sato K. A histopathological study of carcinoma of the larynx. Auris Nasus Larynx [Tokyo] 1985;12[suppl 2]:S173)

TABLE 18-2. Incidence of Cricoid Cartilage Invasion on Whole-Organ Laryngectomy Sections

	T1	T2	T3	T4
Supraglottic	0/1	0/8	0/10	0/2
Glottic	0/2	1/8	4/16	1/1
Subglottic	No data	0/1	0/1	1/1

(Adapted from Kurita S, Hirano M, Matsuoka H, Tateishi M, Sato K. A histopathological study of carcinoma of the larynx. Auris Nasus Larynx [Tokyo] 1985;12[suppl 2]:S174)

Fixation of the vocal cord is usually caused by invasion or destruction of the vocal muscle, invasion of the cricoarytenoid muscle/joint, or, rarely, invasion of the recurrent laryngeal nerve.

Perineural spread is uncommon in laryngeal malignancies.

Supraglottic Larynx

The majority of lesions are epiglottic in origin. It is difficult to assign a site of origin for advanced lesions.

SUPRAHYOID EPIGLOTTIS. Lesions of the suprahyoid epiglottis may grow like a mushroom, producing a huge exophytic mass with little tendency to destruction of cartilage or spread to adjacent structures. Others may infiltrate the tip and produce destruction of cartilage and eventual amputation of the tip. The latter lesions tend to invade the vallecula and preepiglottic space, the lateral pharyngeal walls, and the remainder of the supraglottic larynx. A horizontal whole-organ section from a supraglottic laryngectomy for an early carcinoma of the tip of the epiglottis is shown in Figure 18-5.

INFRAHYOID EPIGLOTTIS. Lesions of the infrahyoid epiglottis tend to produce irregular outgrowths of tumor nodules with simultaneous invasion through the porous epiglottic cartilage and thyroepiglottic ligament into the preepiglottic fat space (Color Fig. 13). Tumor may spread along the preepiglottic fat space, penetrate the hyoepiglottic ligament, and present in the vallecula and base of the tongue without involving the suprahyoid epiglottis.

Lesions of the infrahyoid epiglottis grow circumferentially to involve the false cords, aryepiglottic folds, and eventually the medial wall of the pyriform sinus and the pharyngoepiglottic fold. Invasion of the anterior commissure and cords is usually a late phenomenon, and subglottic extension occurs only in advanced lesions. Infrahyoid epiglottic lesions that extend onto or below the vocal cords are at risk for cartilage invasion, even if the cords are mobile.[67]

FALSE CORD/VENTRICLE. False cord carcinomas are usually infiltrative and ulcerative with little exophytic component and are difficult to delineate accurately. They involve the paraglottic fat space early in their development and may spread a considerable distance beneath the mucosa without producing physical signs; they are therefore often understaged. These carcinomas extend to the perichondrium of the thyroid cartilage quite early, but cartilage invasion is a late phenomenon. Extension to the lower portion of the infrahyoid

Figure 18-5. Sagittal section through supraglottic laryngectomy specimen. Early carcinoma of the tip of the epiglottis (*arrows*) with involvement of the lingual and laryngeal surfaces with minimal cartilage destruction. E, epiglottis; PES, preepiglottic fat space; H, hyoid; T, thyroid cartilage. (Courtesy of A.W. P. van Nostrand, Toronto General Hospital, Ontario, Canada)

epiglottis with invasion of the preepiglottic space is common. Submucosal extension occurs to involve the vocal cord (Color Fig. 14). Vocal cord invasion is often associated with thyroid cartilage invasion. Submucosal extension to the medial wall of the pyriform sinus occurs early. Subglottic extension is uncommon until the lesion is advanced.

ARYEPIGLOTTIC FOLD/ARYTENOID. Early lesions in this location are usually exophytic growths. As the lesions enlarge, they extend to adjacent sites and eventually cause fixation of the larynx. Fixation is usually due to involvement of the cricoarytenoid muscle or joint or rarely to invasion of the recurrent laryngeal nerve. Advanced lesions may invade the thyroid, epiglottic, and cricoid cartilages and eventually spread to the base of the tongue and pharyngeal wall. It may be difficult to decide whether the lesion started on the medial wall of the pyriform sinus or on the aryepiglottic fold.

Vocal Cord

The majority of lesions begin on the free margin and upper surface of the vocal cord (Color Fig. 15). When diagnosed, about two thirds are confined to the cords, usually one cord. The anterior portion of the cord is the most common site, and extension to the anterior commissure is frequent. Anterior commissure involvement is said to occur when no tumor-free cord can be seen anteriorly; when the lesion crosses over to the opposite cord, anterior commissure invasion is certain. Small lesions isolated to the anterior commissure account for only 1% to 2% of all cases.

Early lesions are frequently associated with zones of carcinoma in situ and atypism at the periphery of the lesion, and noncontiguous areas of carcinoma in situ or even early invasive tumor are seen in adjacent sites.

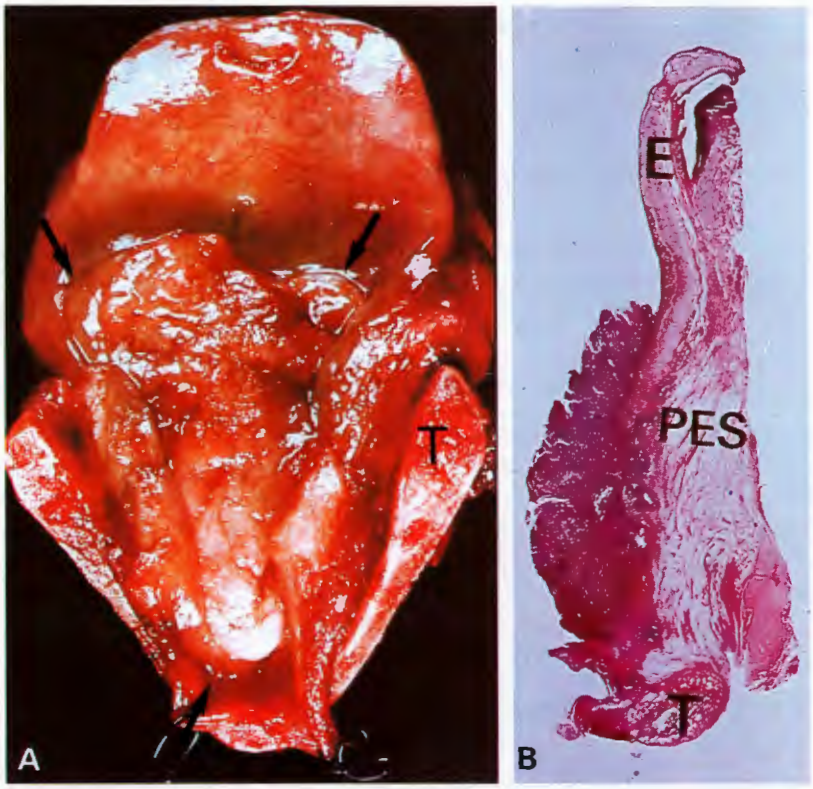
Tumors at the anterior commissure may extend anteriorly the short distance along the anterior commissure tendon (Broyles' ligament), which inserts directly into the thyroid cartilage and thus allows tumor access to the cartilage without the necessity of penetrating either a muscle or the perichondrium.[10] Early subglottic extension is also associated with involvement of the anterior commissure, and tumor may then grow through the cricothyroid membrane.

Lesions that arise on the posterior half of the vocal cord tend to extend along the submucosa toward the medial side of the vocal process to invade the cricoarytenoid joint and interarytenoid area. This extension is difficult to appreciate by clinical examination and results in understaging of the posterior vocal cord lesions. Lesions may spread beneath the epithelium along the length of the vocal cord within Reinke's space.[60] Subglottic extension may occur by simple mucosal surface growth, but also occurs by submucosal penetration through the conus elasticus (Color Fig. 16). One centimeter of subglottic extension anteriorly or 4 to 5 mm of subglottic extension posteriorly brings the border of the tumor near the upper margin of the cricoid.

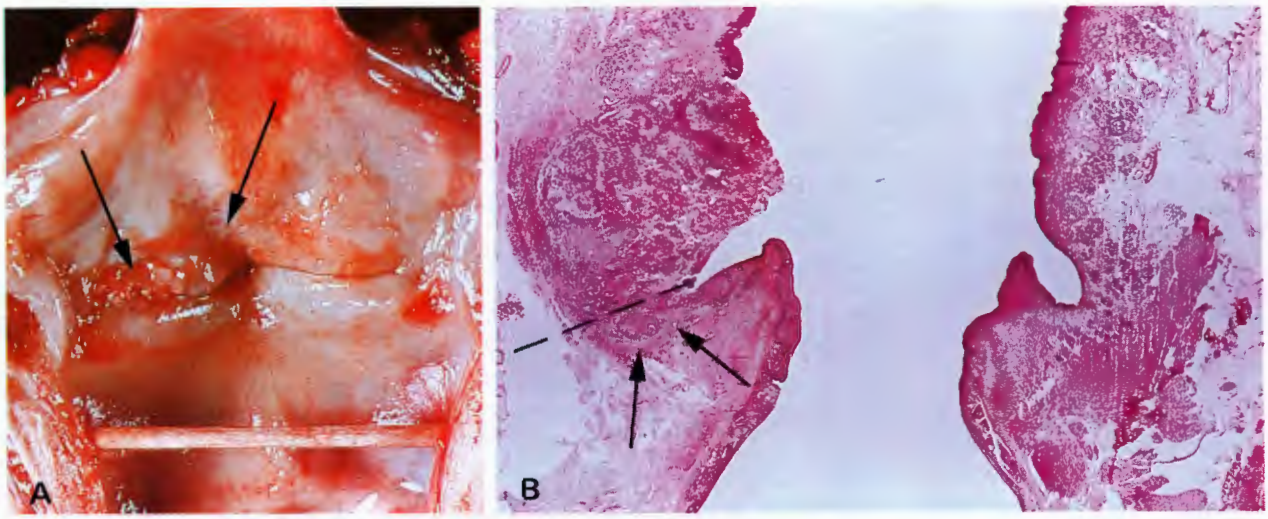
As vocal cord lesions enlarge, they extend to the ventricle/false cord, vocal process of the arytenoid, and subglottic region (Color Fig. 17). Infiltrative lesions invade the vocal ligament and muscle and eventually reach the paraglottic space and then the perichondrium of the thyroid cartilage. Once cancer reaches the perichondrium, it tends at first to grow up or down along the face of the cartilage in the paraglottic space rather than invading the cartilage. The conus elasticus acts only as a temporary barrier to subglottic penetration. The conus elasticus may direct tumor growth toward the thyrocricoid membrane. Advanced glottic lesions eventually penetrate through the thyroid cartilage, cricothyroid membrane, or cricoid cartilage to enter the neck where they may invade the thyroid gland. Lesions involving the anterior commissure often extend through the cricothyroid membrane after they extend subglottically.[60] Extension through the cricothyroid membrane is almost always associated with invasion of the adjacent edges of the thyroid or cricoid cartilage.

A fixed cord with less than 1 cm of subglottic extension and no false cord involvement does not ordinarily predict invasion of the thyroid cartilage.[38] If the false cord is also involved, cartilage invasion is likely.

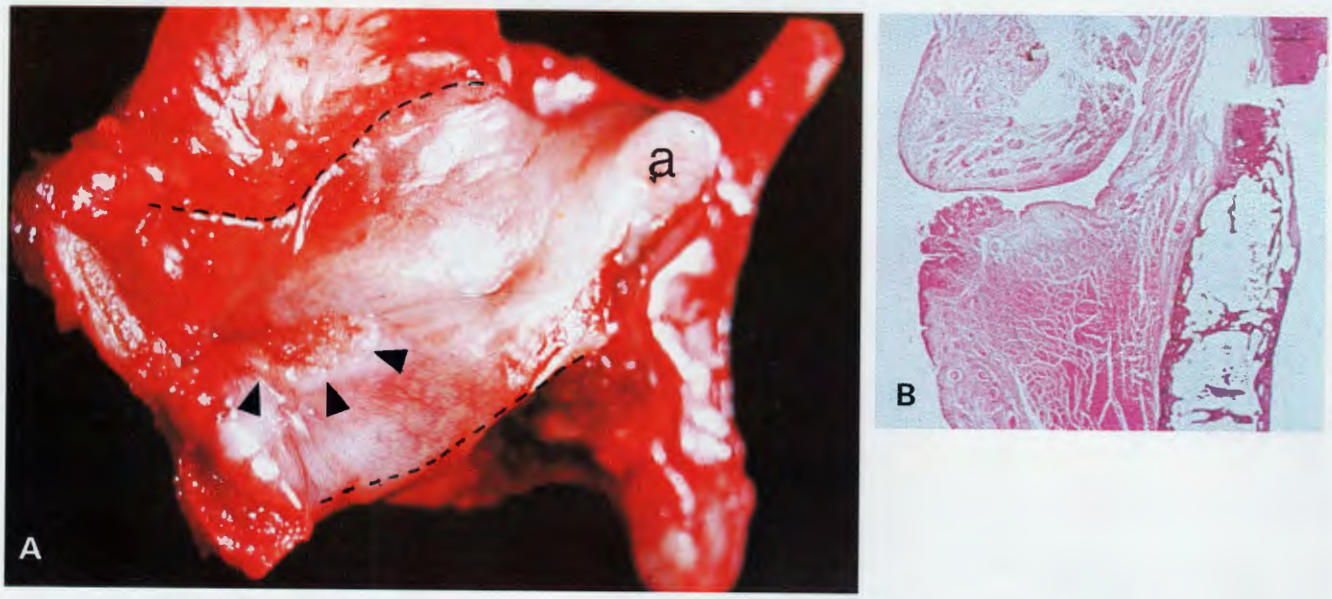
Jesse reported 48 patients whose disease was clinically staged T4.[36] In 47 the cancer was pathologically staged T4 owing to cartilage invasion (54%), cricothyroid



Color Figure 13. Carcinoma of the infrahyoid epiglottis. (*A*) Supraglottic laryngectomy specimen with large lesions (*arrows*) replacing the infrahyoid epiglottis. T, thyroid cartilage. (*B*) Vertical section through specimen. The lesion is mostly exophytic. There is invasion of the thyroepiglottic ligament but minimal invasion of preepiglottic space. T, thryoid cartilage; E, epiglottis; PES, preepiglottic space. (Courtesy of A. W. P. van Nostrand, Toronto General Hospital, Ontario, Canada)



Color Figure 14. (*A*) Total laryngectomy specimen showing an early carcinoma of the left false cord (*arrows*). The left true vocal cord appears grossly normal. (*B*) Coronal section through left false cord shows submucosal extension of the tumor around the angle of the ventricle to the vocal cord. A conventional supraglottic laryngectomy would cut across the tumor. The dashed line shows the usual lower border for supraglottic laryngectomy; arrows point to the tumor margin. (Courtesy of A. W. P. van Nostrand, Toronto General Hospital, Ontario, Canada)



Color Figure 15. (*A*) Hemilaryngectomy specimen showing a carcinoma (*arrows*) confined to the anterior true vocal cord. Note the mucosal margins of resection (*dashed lines*). The inferior margin of resection corresponds to the top of the cricoid cartilage; the subglottic margin anteriorly is about 1.5 cm below the free margin of the vocal cord, gradually tapering to about 1.0 mm posteriorly. The superior mucosal cut corresponds to the superior border of the thyroid cartilage and would be 1.5 to 2.0 cm above the free margin of the vocal cord. The posterior border includes the arytenoid (a) in this specimen; the arytenoid is usually not removed unless necessary to obtain a margin. (*B*) Coronal section showing lesion confined to margin of cord with minimal invasion. (Olofsson J, van Nostrand AWP: Growth and spread of laryngeal and hypopharyngeal carcinoma with reflections on the effect of preoperative irradiation. Acta Otolaryngol [Suppl] 1973;308:21)

perforation (54%), extension to the pharyngeal wall (38%), or extension to or below the first tracheal ring (60%).

Subglottic Larynx

Subglottic cancers are rare. Most of them involve the vocal cords by the time they are diagnosed, so it is difficult to know whether the tumor started on the undersurface of the vocal cord or in the true subglottic larynx. The lesions are bilateral or circumferential in most instances since early diagnosis is uncommon. They involve the cricoid cartilage early, since there is no intervening muscle layer. Penetration through the cricothyroid membrane occurs early with tumor extending into the anterior soft tissues of the neck and into the thyroid gland. Partial or complete fixation of one or both cords is common. Tracheal extension occurs frequently.

Lymphatic Spread

Supraglottic Larynx

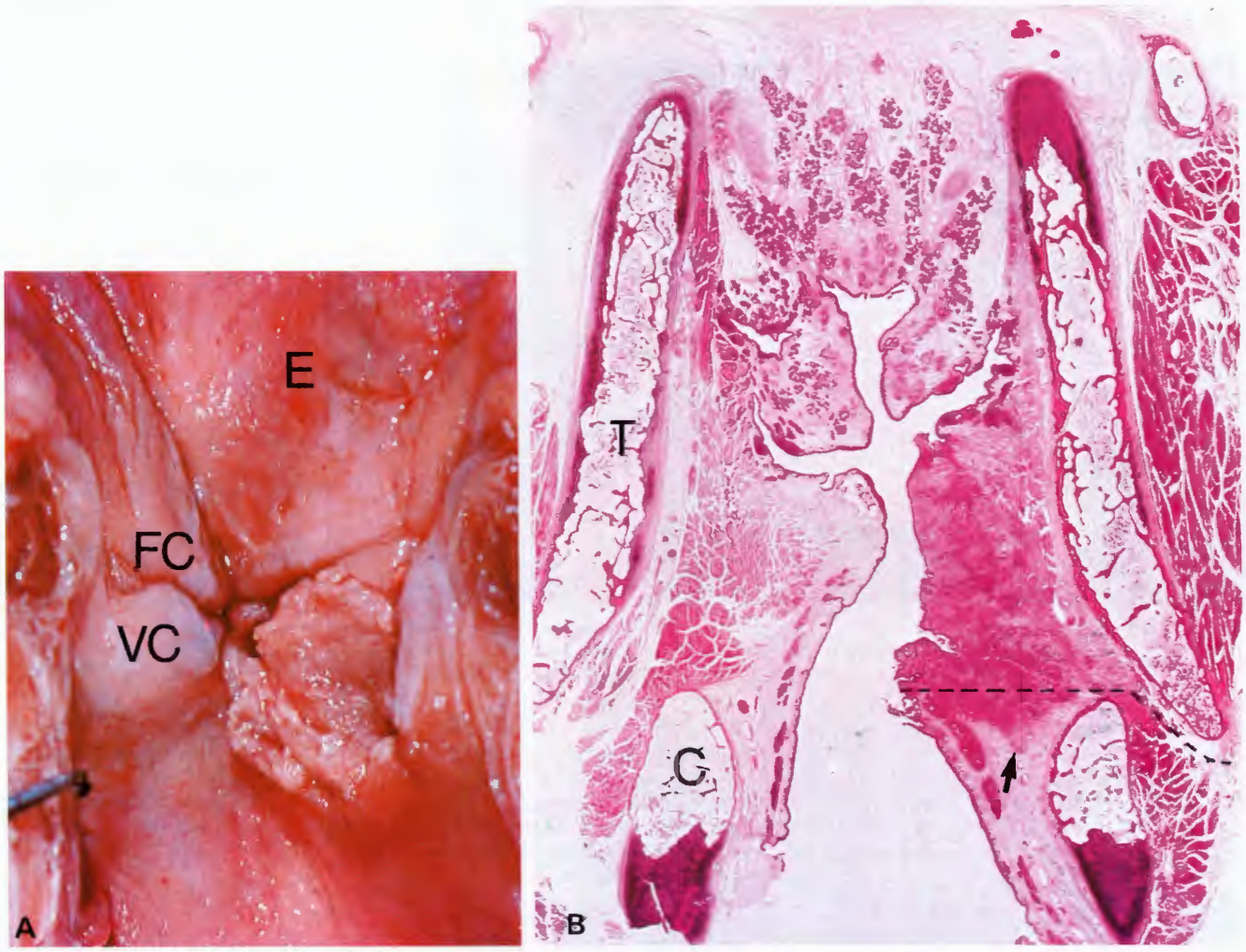
The distribution and N staging on admission before treatment for previously untreated patients with squamous cell carcinoma of the supraglottic larynx are given in Figure 18-6.[43] The spread pattern is mainly to the subdigastric area and internal jugular vein chain. The submandibular area is rarely involved, and there is only a small risk for spinal accessory lymph node involvement.

The incidence of clinically positive nodes is 55% at the time of diagnosis; 16% are bilateral.[43] Elective neck dissection will show pathologically positive nodes in about 25% of cases. The rate for stage T1–T2 was 31% and for stage T3–T4 it was 25%. Observation of the neck will be followed by the appearance of positive nodes in 33% of cases.[16,56] The distribution of positive lymph nodes for 93 elective neck dissections is shown in Figure 18-7.[11] Note the 10% involvement of the lateral paratracheal nodes. Extralaryngeal spread to the pyriform sinus and vallecula/base of the tongue increases the risk of node metastases. The risk of late-appearing contralateral lymph node metastasis is 37% when the ipsilateral neck is pathologically positive. The risk is unrelated to whether the nodes in the ipsilateral neck were palpable before neck dissection. The finding of an involved Delphian lymph node is rare.[61]

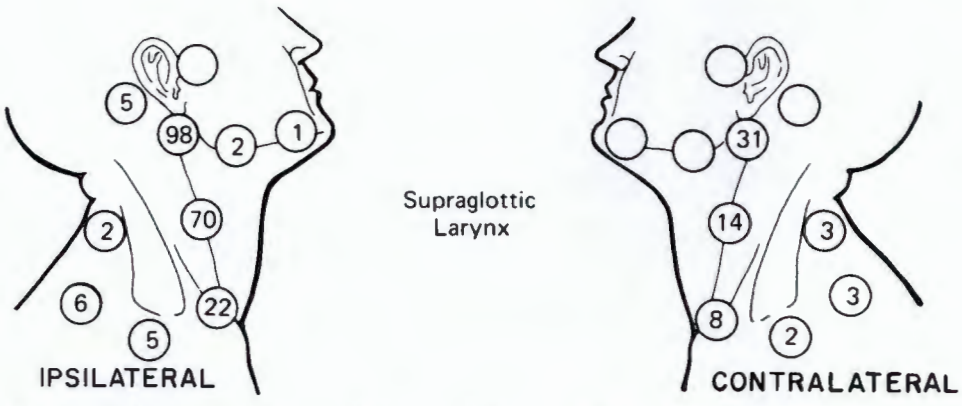
Vocal Cord

The reported incidence of clinically positive lymph nodes at diagnosis approaches zero for lesions confined to the cords (T1) and is 2% to 7% for T2 lesions.

Mendenhall and associates reviewed the risk of neck disease for 98 patients with T2N0 squamous cell carcinoma of the glottic larynx (Table 18-3). Irradiation portals were planned to cover only the primary lesion; the Delphian lymph nodes were in the high-dose area. The midjugular lymph nodes would be on the edge of the portal and would not receive sufficient dose for subclinical disease. When the primary site was continuously free

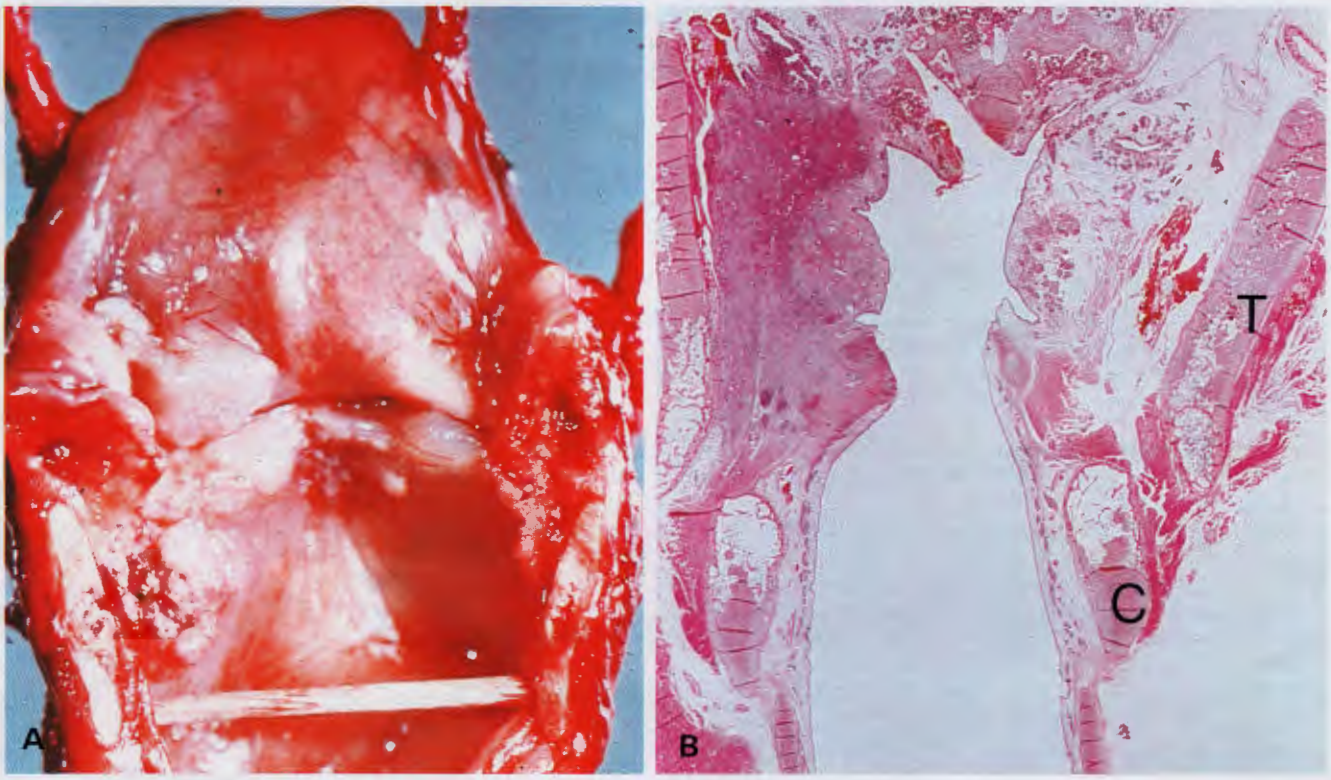


Color Figure 16. (*A*) Total laryngectomy specimen shows a carinoma of the entire right vocal cord with obvious subglottic extension and invasion of the anterior commissure (T2). FC, left false cord; VC, left true vocal cord; E, epiglottis. (*B*) Whole-organ coronal section at mid cord level. The right vocal muscle is largely destroyed, and the tumor has penetrated the conus elasticus to involve the subglottic area. There is early involvement of the paraglottic fat space; note slight narrowing of space on the right compared with the left. There is no extension to the thyroid (T) or cricoid (C) cartilages. Dashed line shows the limits of conventional hemilaryngectomy. Arrow points to tumor margin. A portion of the cricoid would have to be removed to obtain a margin. (Olofsson J, van Nostrand AWP: Growth and spread of laryngeal and hypopharyngeal carcinoma with reflections on the effect of preoperative irradiation. Acta Otolaryngol [Suppl] 1973;308:22)



N_0	N_1	N_{2A}	N_{2B}	N_{3A}	N_{3B}	N_1–N_3 / Total
120	49	15	29	11	43	147 / 267 = 55%

Figure 18-6. Nodal distribution on admission, M. D. Anderson Hospital, 1948–1965. (Lindberg RD. Distribution of cervical lymph node metastases from squamous cell carcinoma of the upper respiratory and digestive tracts. Cancer 1972;29:1449)



Color Figure 17. (*A*) Total laryngectomy specimen of an extensive vocal cord carcinoma with fixed left vocal cord (T3). There is obvious extension to the supraglottic and subglottic areas on the left with involvement of the anterior commissure and anterior half of the right vocal cord. (*B*) Coronal section at mid cord level. There is extensive invasion of the left false cord. The paraglottic space is replaced by the tumor. Involvement of the subglottic area on this section is minimal. There is no invasion of cartilage. C, cricoid cartilage; T, thryoid cartilage. (Courtesy of A. W. P. van Nostrand, Toronto General Hospital, Ontario, Canada)

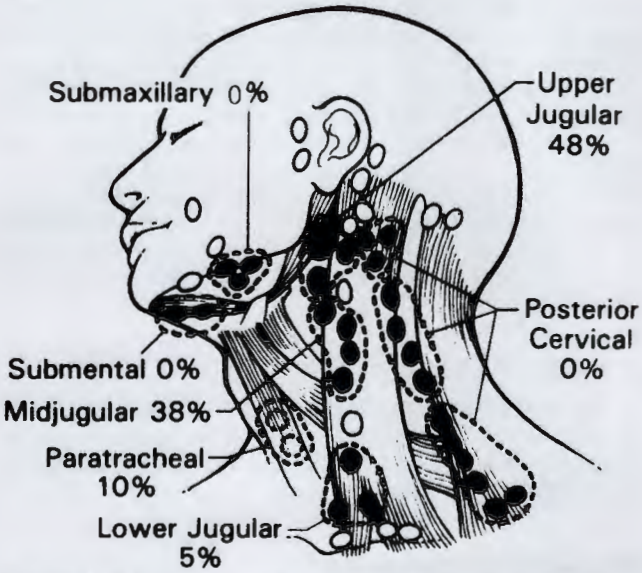


Figure 18-7. Distribution of positive neck nodes in elective neck dissections in 93 patients with carcinoma of the supraglottic larynx. (Byers RM, Wolf PF, Ballantyne AJ. Rationale for elective modified neck dissection. Head Neck Surg 1988;10:164)

of recurrence, 3% of patients developed a neck node: 2% with normal vocal cord mobility and 3% with reduced mobility. With local recurrence, however, the risk increased to 22%, which is similar to the 20% risk of neck disease in recurrent T1 lesions.[46]

The incidence of neck metastases on admission is about 20% for T3 and T4 lesions. Mendenhall and associates reported a 16% incidence of subclinical disease with elective neck dissection in 25 patients with T3N0 vocal cord carcinoma.[50] Byers and coworkers reported a 14% incidence of involved lymph nodes for elective neck dissection in 57 T3–T4 glottic lesions. The distribution of involved lymph nodes after elective neck dissection is shown in Figure 18-8.[11] Note the risk of lateral paratracheal lymph node involvement. Supraglottic spread is associated with metastasis to the jugulodigastric nodes. Anterior commissure and anterior subglottic invasion is associated with mid and low jugular chain, midline pretracheal (Delphian node), and lateral paratracheal lymph node involvement.

Sessions and associates reviewed 132 glottic carcinomas with subglottic extension (more than 5 mm below the free margin of the vocal cord). Only five patients had clinically positive lymph nodes on admission, in spite of the fact that 61% had more than 1 cm of subglottic exten-

TABLE 18-3. T2N0 Squamous Cell Carcinoma of the True Vocal Cord Treated by Radiation Therapy: Control of Disease in the Neck in 98 Patients (No. Controlled/No. Patients Treated)

Primary Site Continuously Disease Free	Surgical Alternative	Initial Control of Neck Disease	No. Salvaged/ No. Attempted	Ultimate Control of Neck Disease
Yes	Hemilaryngectomy	35/36 (97%)	0/1	35/36 (97%)
	Total laryngectomy	38/39 (97%)	0/1	38/39 (97%)
No	Hemilaryngectomy	5/9	3/4	8/9
	Total laryngectomy	13/14	1/1	14/14

(Mendenhall WM, Parsons JT, Brant TA, Stringer SP, Cassisi NJ, Million RR. Is elective neck treatment indicated for T2N0 squamous cell carcinoma of the glottic larynx? Radiother Oncol 1989;14:201)

sion and 20% had more than 2 cm of subglottic extension. Only four patients died because of uncontrolled neck disease alone.[71]

Olsen reported 13 patients with involved Delphian lymph nodes (T1, 3 patients; T2, 2 patients; T3, 8 patients). Delphian involvement correlated with anterior commissure and subglottic extension and recurrence after radiation therapy or surgery. Six of 13 patients with Delphian node involvement developed neck recurrence after surgery and all died of cancer.[61]

Subglottic Larynx

Lederman reported a 10% incidence of positive lymph nodes in 73 patients with subglottic carcinoma.[40] Olsen and coworkers reported four patients with primary subglottic carcinomas and an involved Delphian lymph node; all died of cancer after laryngectomy.[61] Harrison reported a high incidence of lymph node involvement, especially the paratracheal lymph nodes, with subglottic carcinomas. He noted, however, that it was rare to find more than an occasional paratracheal lymph node after curative radiation therapy.[29] Guedea and associates reviewed six cases of subglottic cancer and none had clinically invaded lymph nodes.[26] Shaha and Shah reported that none of 12 T1–T2 lesions had clinically involved lymph nodes but two of four T4 lesions were clinically positive.[73]

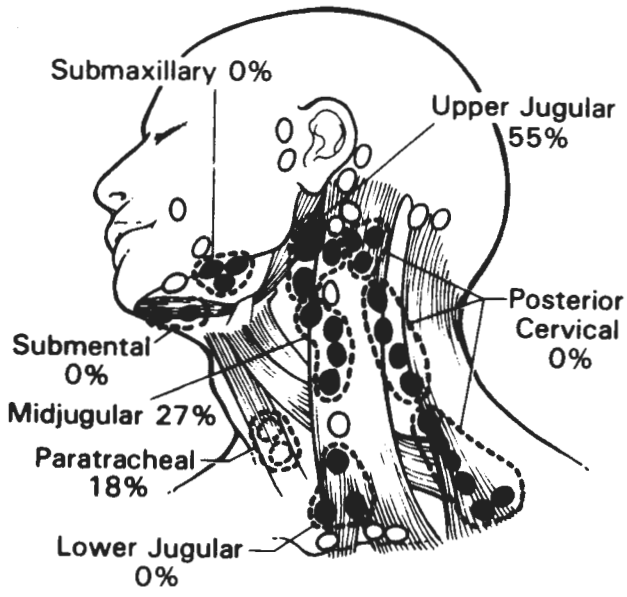


Figure 18-8. Distribution of positive neck nodes in elective neck dissections in 57 patients with carcinoma of the glottic larynx. (Byers RM, Wolf PF, Ballantyne AJ. Rationale for elective modified neck dissection. Head Neck Surg 1988;10:164)

CLINICAL PICTURE

Presenting Symptoms

Vocal Cord

Carcinoma arising on the true vocal cords produces hoarseness as the initial symptom. Sore throat, ear pain, pain localized to the thyroid cartilage, and airway obstruction are features of advanced lesions.

Supraglottic Larynx

Hoarseness is not a prominent symptom for cancer of the supraglottic larynx until the lesion becomes quite extensive. Changes in voice quality are often described as a "hot potato" quality, the voice quality associated with unexpectedly swallowing a bite of hot food. Pain on swallowing, usually mild, is the most frequent initial symptom. The pain is often described as a mild, persistent irritation or sore throat, and often the patient can point to the area with one finger. Mild difficulty in swallowing is frequent, and some patients report a sensation of a "lump in the throat." Cancer of the epiglottis may be quite large before symptoms are produced. Pain is referred to the ear by way of the vagus nerve and auricular nerve of Arnold (see Fig. 16-16). A mass in the neck may be the first sign of a supraglottic cancer. Late symptoms include weight loss, foul breath, dysphagia, and aspiration.

Subglottic Larynx

The symptoms are similar to those for cancer of the glottic larynx. Hoarseness is the most common early symptom followed by dyspnea and stridor caused by airway obstruction.

Physical Examination

Rigid and flexible fiberoptic illuminated endoscopes are now used routinely as a complement to the laryngeal mirror examination (see Chap. 3).

A horseshoe-shaped epiglottis or a posterior lying epiglottis may prohibit adequate laryngeal examination for even the most skilled examiner. The tip of the epiglottis may be amputated to facilitate indirect examination of the larynx (Fig. 18-9). This is performed at the time of direct laryngoscopy. Loss of the tip of the epiglottis does not result in functional problems.

Determination of the mobility of the vocal cords frequently requires multiple examinations, since the subtle distinctions between mobile, partially fixed, and fixed cords are often difficult and in fact seem to change from examination to examination. A cord that appeared mobile to the surgeon before direct laryngoscopy may show sluggish motion or even fixation after biopsy. Invasion of the preepiglottic space occurs more frequently than can be diagnosed clinically. Ulceration of the infrahyoid epiglottis or fullness of the vallecula is an indirect sign of preepiglottic space invasion. Palpation of diffuse, firm fullness above the thyroid notch with widening of the space between the hyoid and thyroid cartilages signifies invasion of the preepiglottic space. Lateral soft tissue roentgenograms of the neck may show the presence of irregular air cavities inferior to the vallecula in patients with lesions of the suprahyoid epiglottis invading into the preepiglottic space by way of the vallecula. The preepiglottic space is readily assessed by CT and MRI.

Postcricoid extension may be suspected when the laryngeal click disappears on physical examination. The thyroid cartilage protrudes anteriorly, producing a picture of fullness of the neck. The diagnosis is confirmed by direct laryngoscopy and diagnostic imaging.

Invasion of the thyroid cartilage remains a difficult clinical diagnosis. Localized pain or tenderness to palpation over one ala of the thyroid cartilage is suggestive. Tumor may penetrate the thyroid ala and be felt as a small subcutaneous mass.

Figure 18-9. Early squamous cell carcinoma of the vocal cord in a 60-year-old woman. The larynx was very small, and the tip of the epiglottis rested against the posterior pharyngeal wall and prohibited outpatient examination of the larynx. The right half of the tip was amputated with a biopsy forceps. This photograph was taken 1 year after radiation therapy. The patient was free of disease at 14 years. (For color photograph see Color Fig. 1*A* in Chapter 3.)

METHOD OF DIAGNOSIS AND STAGING

Staging Procedures

Staging procedures for laryngeal cancer include the following:

- Indirect laryngoscopy (with photography)
- CT scan with contrast media enhancement with supplemental MRI in selected cases (imaging before biopsy)
- Direct laryngoscopy with biopsy
- Chest roentgenogram

Imaging

In past years, laryngeal imaging was done by xeroradiography, plain film tomography, and contrast laryngography. These imaging techniques have been replaced by CT and MRI, which should be done before biopsy.

Technique of Examination

CT and MRI techniques are reviewed in Chapter 4. The neck should always be slightly hyperextended so that the larynx is drawn higher in the neck to help avoid artifacts produced by the shoulders. Patients should be immobilized. The plane of section for laryngeal and hypopharyngeal studies *must* be parallel to the true vocal cords. This angle is selected from the preliminary lateral digital radiograph. Sections made at other angles relative to the true vocal cord can cause major interpretative errors. Such skewed images may make the false cords appear to be at the same level as the undersurface of the true cords. It is essential that sections no more than 3 to 4 mm in thickness be used in laryngeal studies. Occasionally, 1.5 or 2 mm sections can be used at the false cord, true vocal cord, and subglottic region, where 2 or 3 mm of tumor spread might make a difference in treatment. The field of view must be magnified to optimize spatial resolution. Such a technique will allow routine visualization of fine detail such as the paraglottic space at the level of the true cords and improve the visualization of laryngeal skeletal detail. Intravenous contrast medium is used for all studies in laryngeal cancer patients. Many primary tumors will be enhanced, especially at their margins, and this will improve the tumor's conspicuousness, especially at tumor–muscle interfaces. This effect is most noticeable in supraglottic and hypopharyngeal primary lesions or in any tumor that is ulcerative.

MRI studies should be done with receiver coils custom designed to study the neck. Small loop or surface coils meant to study the spine are not adequate. The use of intravenous paramagnetic contrast media is individualized.

Imaging of the Normal Anatomy

CT imaging of the normal larynx is shown in Figures 18-10 through 18-12.[44]

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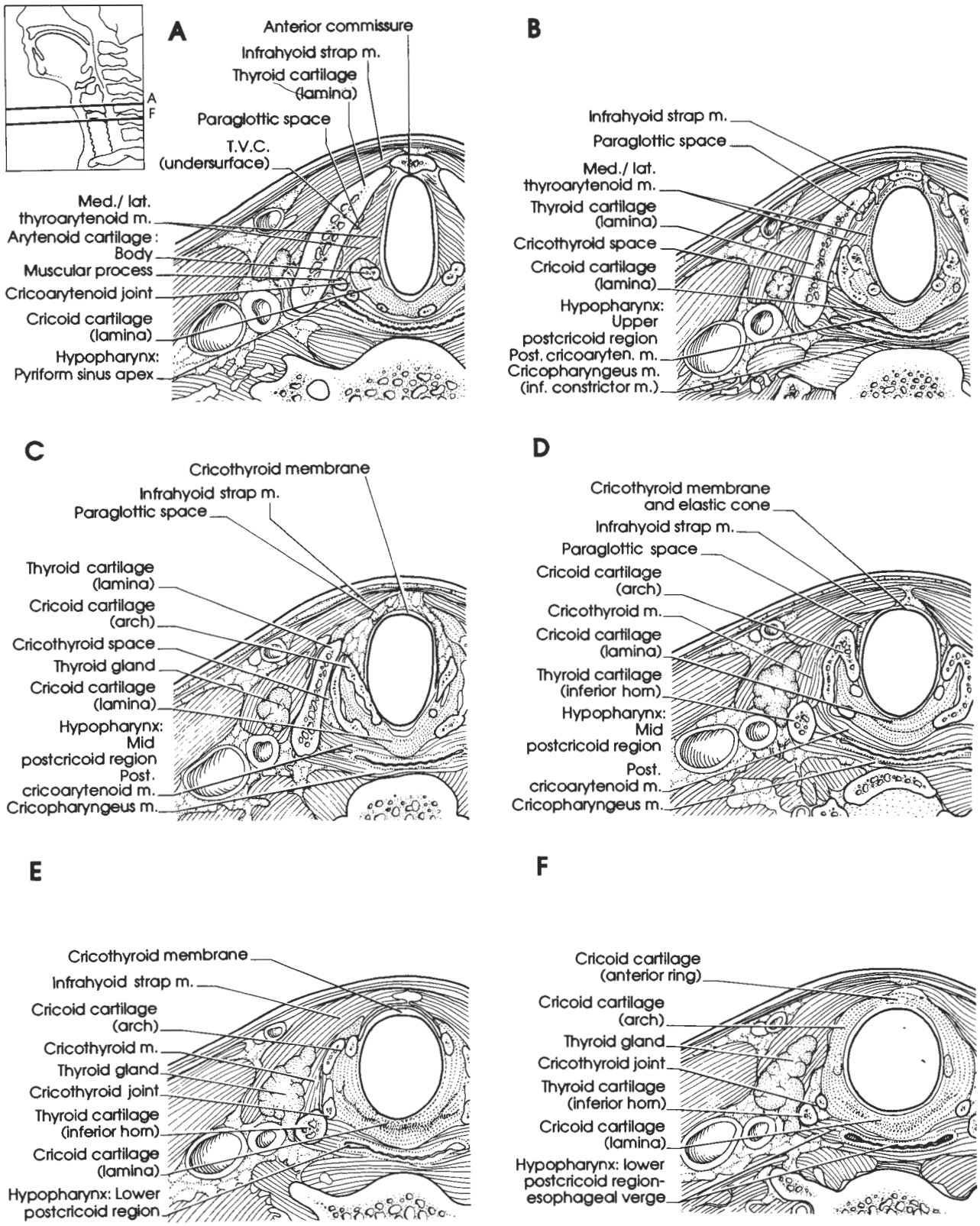

Figure 18-10. (*A* through *F*) CT sections from the undersurface of the true vocal cords to the cricotracheal junction levels. Accompanying line diagrams highlight the pertinent anatomy. (Modified from Mancuso AA, Harnsberger HR, Dillon WP. Workbook for MRI and CT of the head and neck, ed 2. Baltimore, Williams & Wilkins, 1989:176–179)

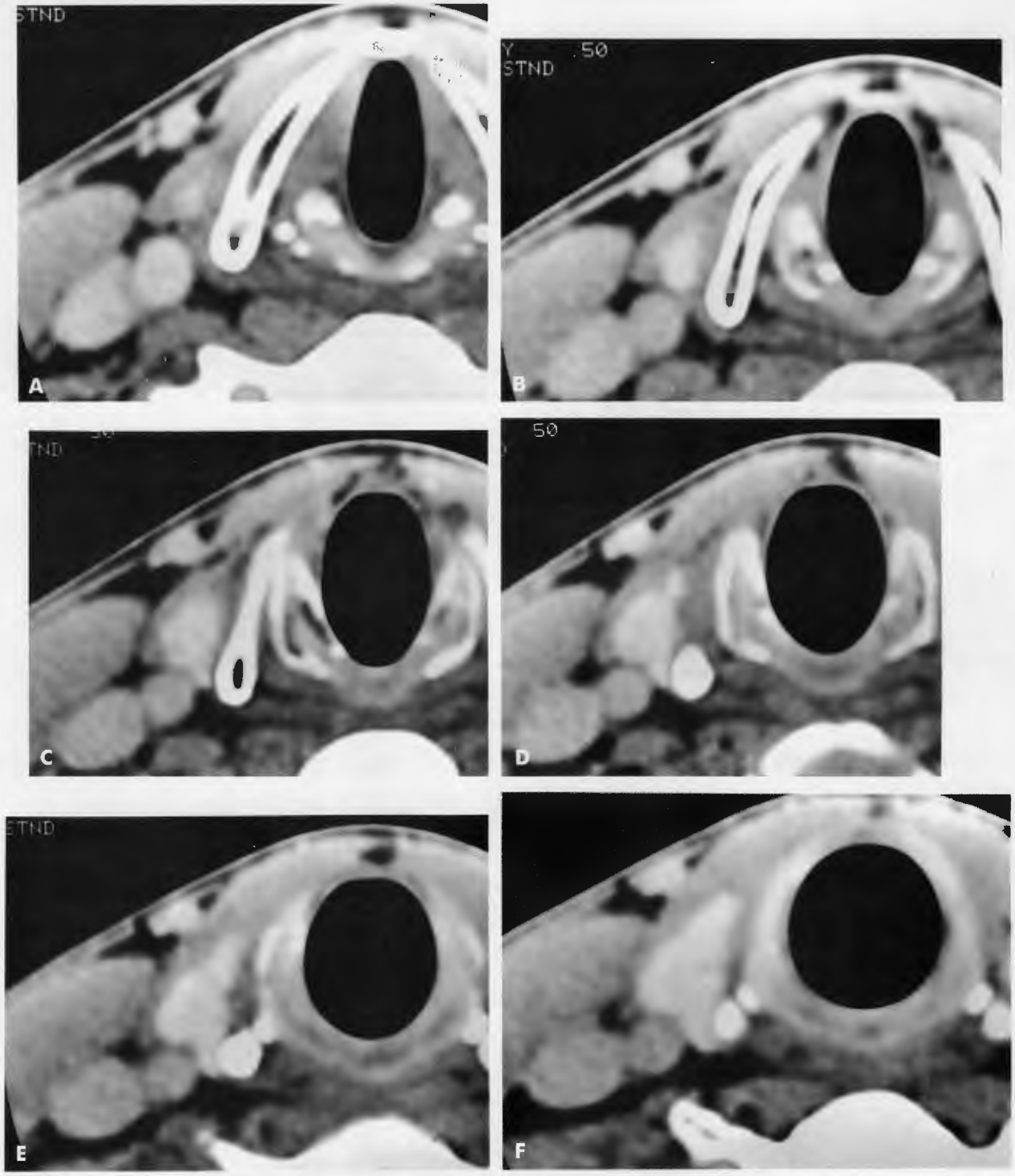

Figure 18-10. (*Continued*)

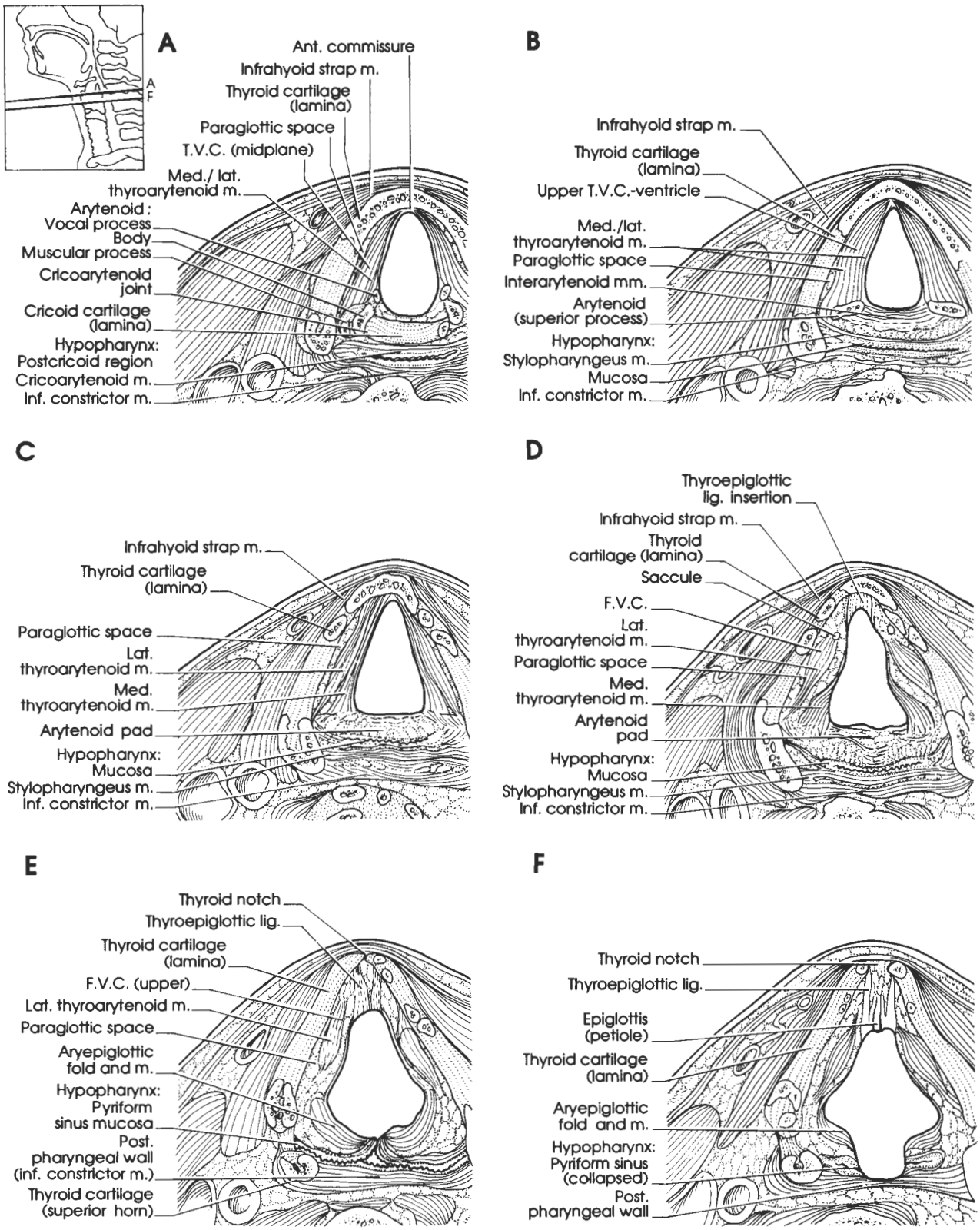

Figure 18-11. (*A* through *F*) CT sections from the true cord level through the laryngeal ventricle and false cords. Accompanying line diagrams illustrate pertinent anatomy at each level. (Modified from Mancuso AA, Harnsberger HR, Dillon WP. Workbook for MRI and CT of the head and neck, ed 2. Baltimore, Williams & Wilkins, 1989:176–179)

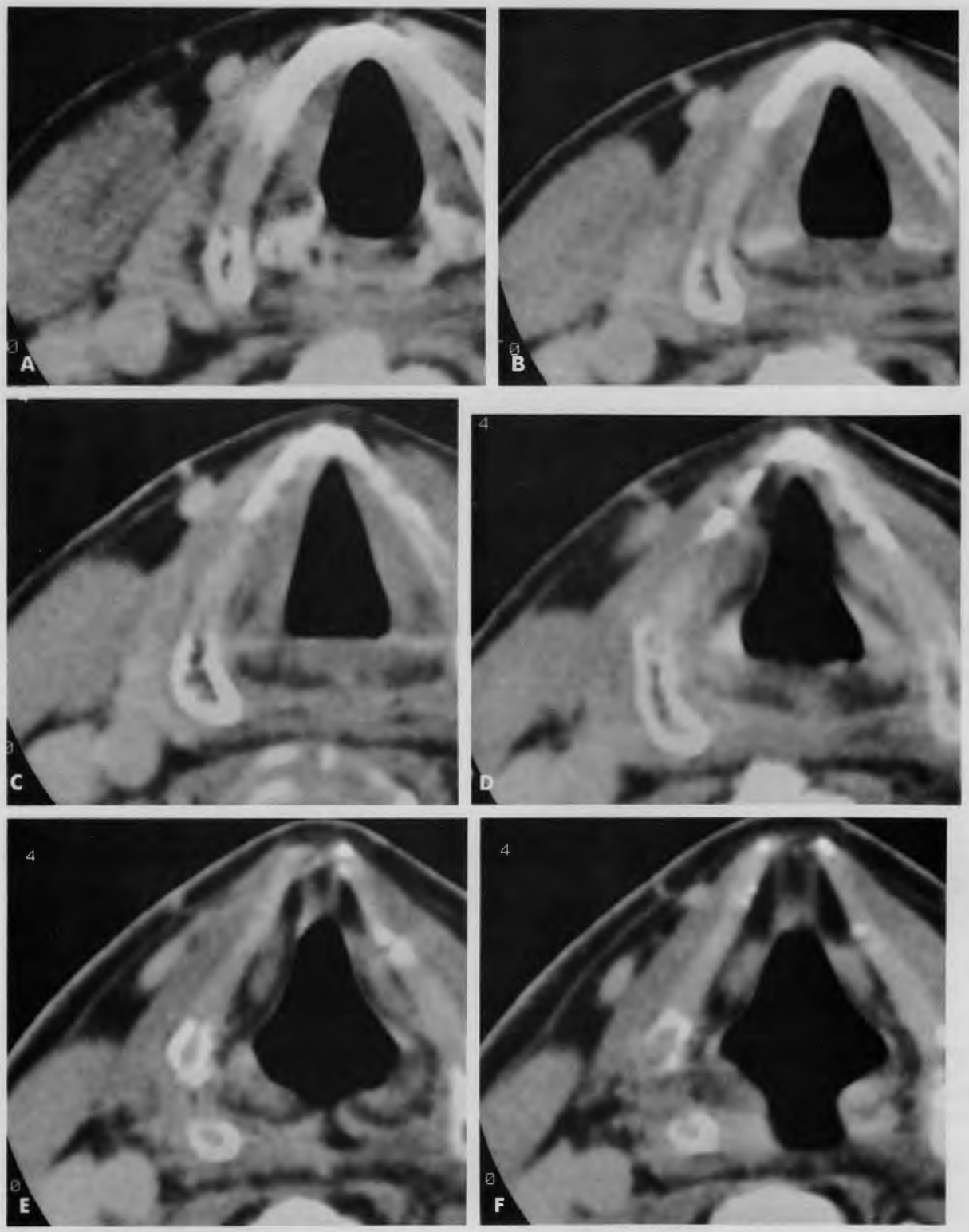

Figure 18-11. (*Continued*)

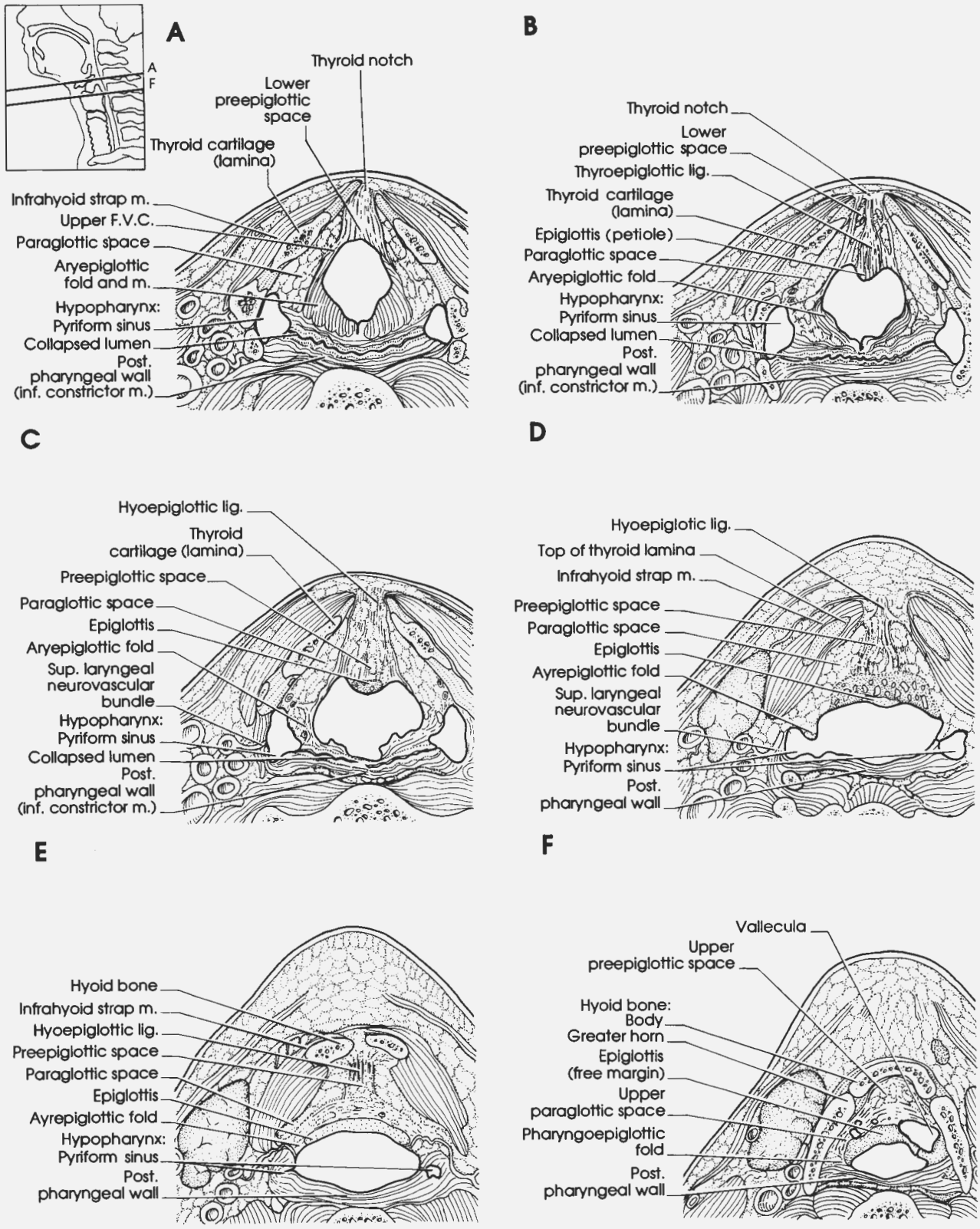

Figure 18-12. (*A* through *F*) CT sections from the level of the false cords to the valleculae. Accompanying line diagrams indicate pertinent normal anatomic structures. (Modified from Mancuso AA, Harnsberger HR, Dillon WP. Workbook for MRI and CT of the head and neck, ed 2. Baltimore, Williams & Wilkins, 1989:176–179)

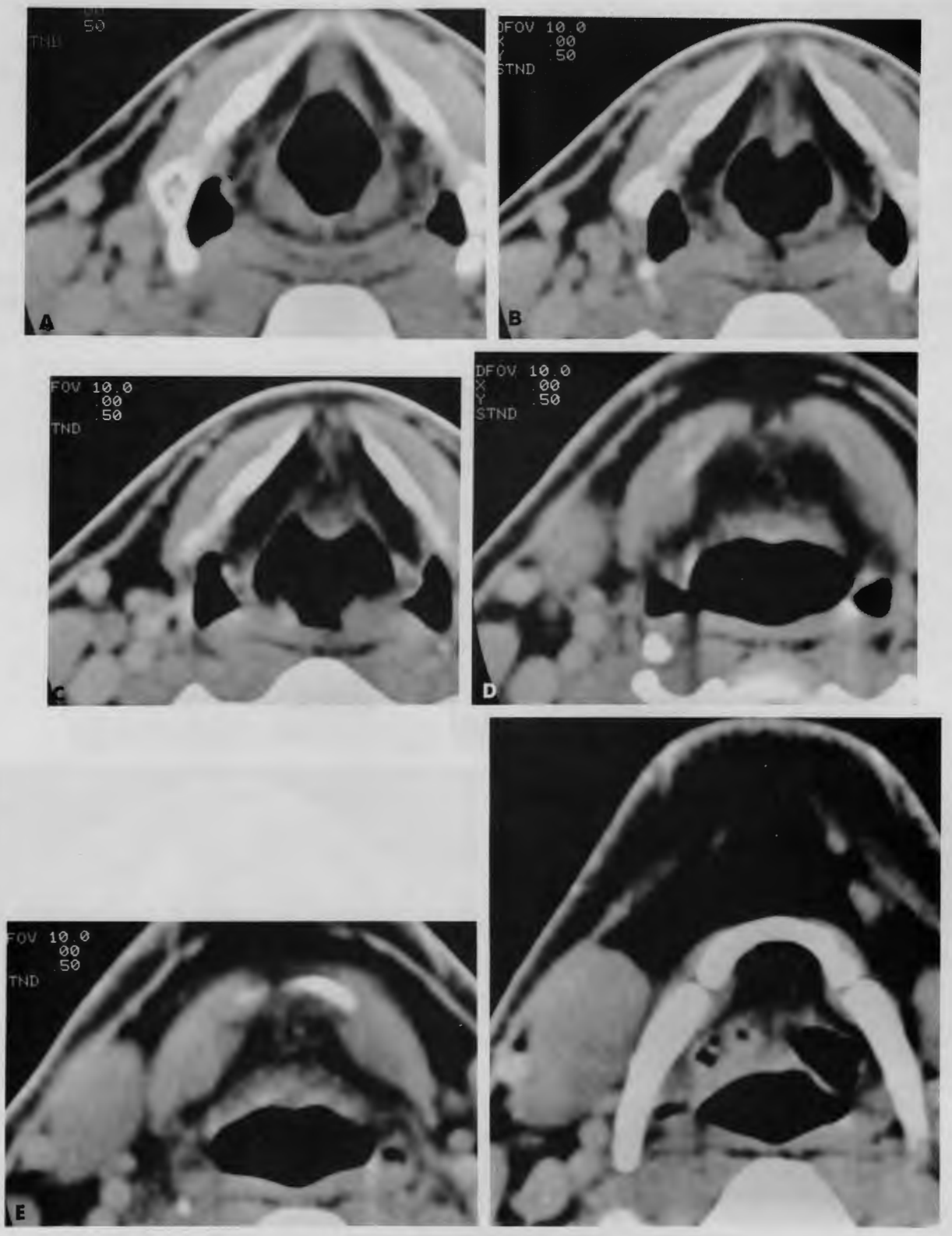

Figure 18-12. (*Continued*)

Indications for Study

T1 lesions of the true cord do not usually require imaging. Any tumor that is suspicious for deep infiltration should be studied primarily with CT. Supplemental MRI study is directed by CT findings to a localized area of interest where its strengths related to soft tissue contrast resolution and multiplanar imaging may be exploited. A large proportion of MRI studies will be of poor quality owing to motion artifacts.

Imaging is useful to evaluate the following regions of interest:

- Tongue base
- Preepiglottic space (Fig. 18-13)
- Paraglottic space (Fig. 18-14)
- Subglottis (Fig. 18-15)
- Cartilage. CT and MRI have limited capability in diagnosing subtle cartilage invasion. Suspicious or high-risk sites are evaluated with 1.5- to 2.0-mm sections processed for bone as well as soft tissue detail. Some reports have suggested that MRI is better than CT for detection of cartilage invasion. It is best to assume that neither CT nor MRI is foolproof and to use both studies with *optimal* techniques. The variation in ossification of the cartilages makes interpretation difficult. Tissue averaging may give a false impression of cartilage defect. Foci of cartilage/bone invasion larger than 5 to 7 mm should be visible or strongly suggested if imaging techniques are adequate. One must take a multifactorial approach to detect early invasion, including the following issues:
- Location and size of the primary tumor

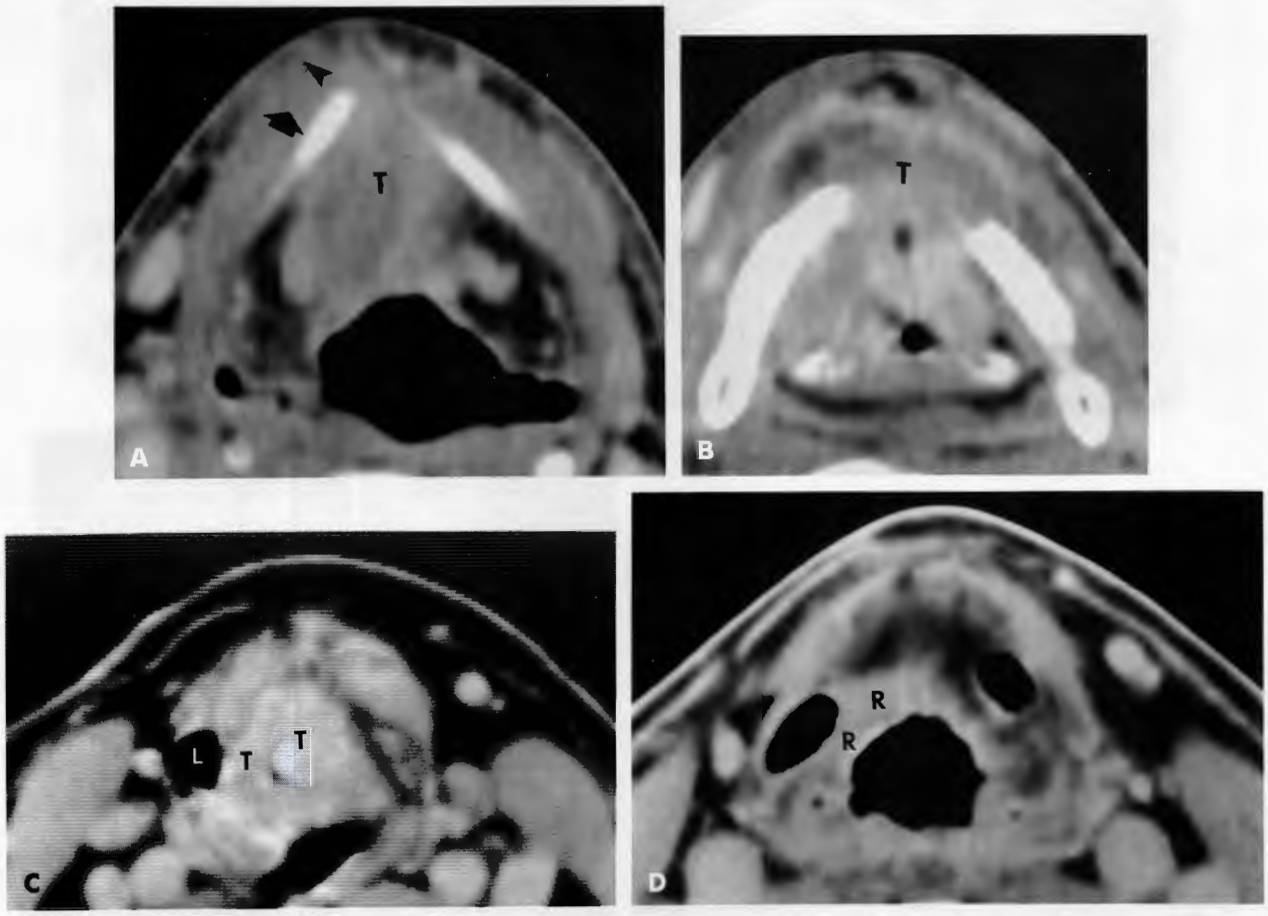

Figure 18-13. Carcinoma of the infrahyoid epiglottis. (*A*) In the first patient, physical examination revealed no anterior neck tenderness nor palpable prelaryngeal mass, but tumor did involve the anterior commissure. Tumor (T) fills the preepiglottic space. It extends slightly more into the right than into the left. The soft planes outside the larynx are abnormal with evidence of spread of tumor to the infrahyoid strap muscles on the right (*arrow*) and edema or tumor involving the subcutaneous fat (*arrowhead*). (*B*) Section taken at the level of the laryngeal ventricle shows tumor (T) destroying the thyroid cartilage and extending into the prelaryngeal soft tissues. CT findings change clinical staging from T2 to T4. In retrospect, some examiners felt "a vague prelaryngeal mass," but there was still no tenderness present. All findings were confirmed at surgery. (*C*) A second patient with a high volume of supraglottic carcinoma within the preepiglottic space. Section performed before radiation therapy at the mid supraglottic levels shows tumor (T) filling the preepiglottic and right paraglottic spaces. A small laryngocele (L) is also present. (*D*) CT scan 4 years after radiotherapy. Small stable residual lesion (R) is most likely fibrosis. The aryepiglottic folds remain thickened because of fibrosis and edema. Patient is alive with no evidence of disease at 6 years.

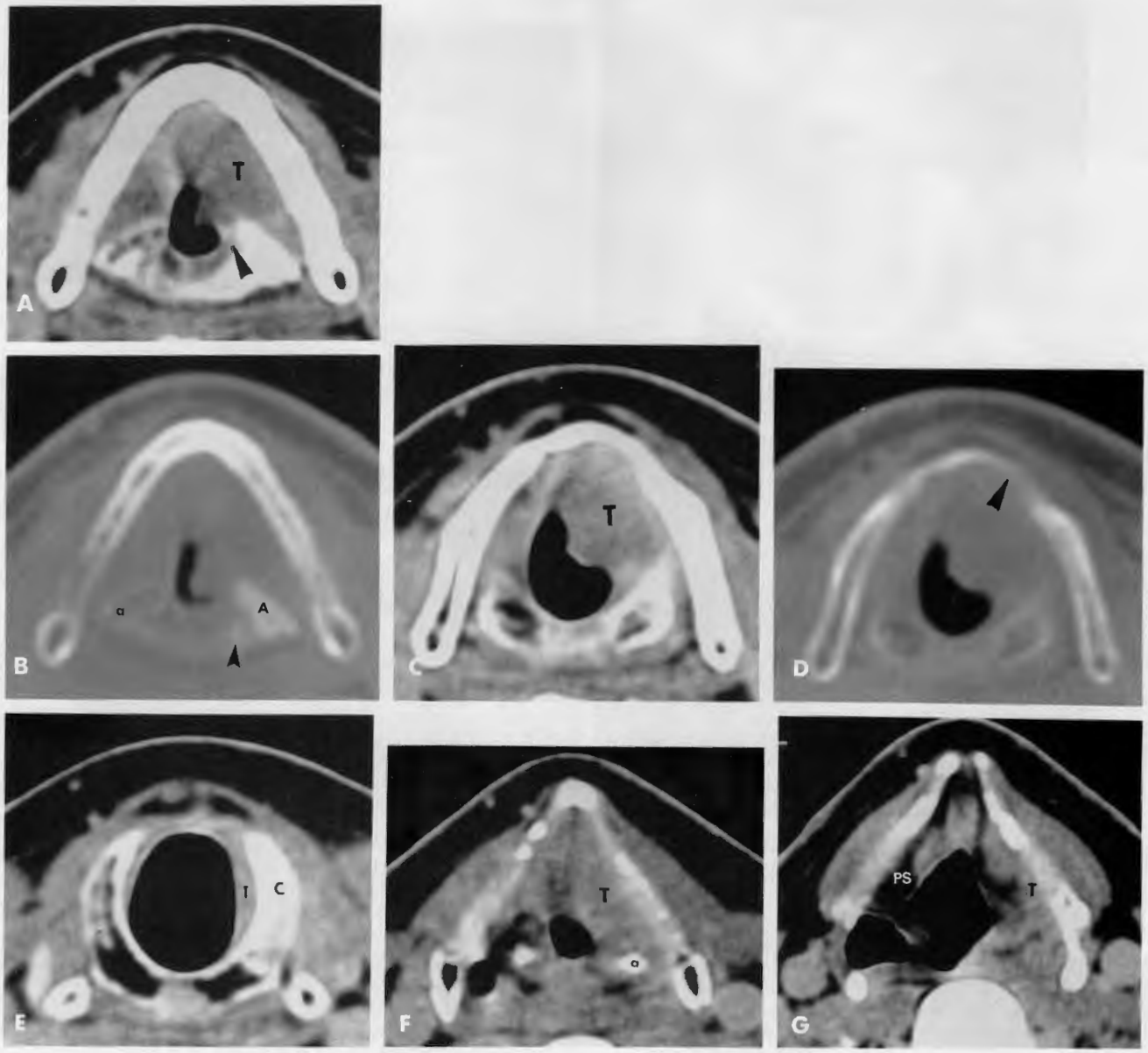

Figure 18-14. Clinical stage T3 carcinoma of the left true vocal cord. (*A*) Section through the true cord level shows tumor (T) enlarging the left true vocal cord and spreading over the medial aspect of the cricoarytenoid joint (*arrowhead*). (*B*) Bone window at the same level as the section in *A*. Note that the left arytenoid (A) is sclerotic compared with the normal right arytenoid (a). There also appears to be some subtle sclerosis of the upper margin of the cricoid cartilage on the left side (*arrowhead*). (*C*) A section through undersurface of the true cord shows a high volume of upper subglottic tumor (T) spreading across the midline anteriorly. (*D*) Bone windows at the same plane as section seen in *C* showing that the thyroid cartilage is thinned (undergoing regressive remodeling) but is not definitely eroded by tumor (*arrowhead*). (*E*) Continued subglottic spread of tumor (T). The sclerosis and obliteration of the marrow space of the left side of the cricoid cartilage (C) are strongly suggestive of invasion but could also be due to reactive sclerosis from adjacent tumor (T). (*F*) At the level of the laryngeal ventricle, there is obliteration of the paraglottic space by tumor (T). Especially note the loss of the tissue planes surrounding the superior process of the arytenoid (a) on the left compared with the normal fat planes on the right. (*G*) Section through false cords shows en plaque spread of tumor (T) adjacent to left thyroid cartilage obliterating the paraglottic space; compare with normal paraglottic space (PS) on the right side. The irregularity of the adjacent thyroid cartilage is not indicative of erosion. Note that the cartilage has an identical appearance on the normal opposite side.

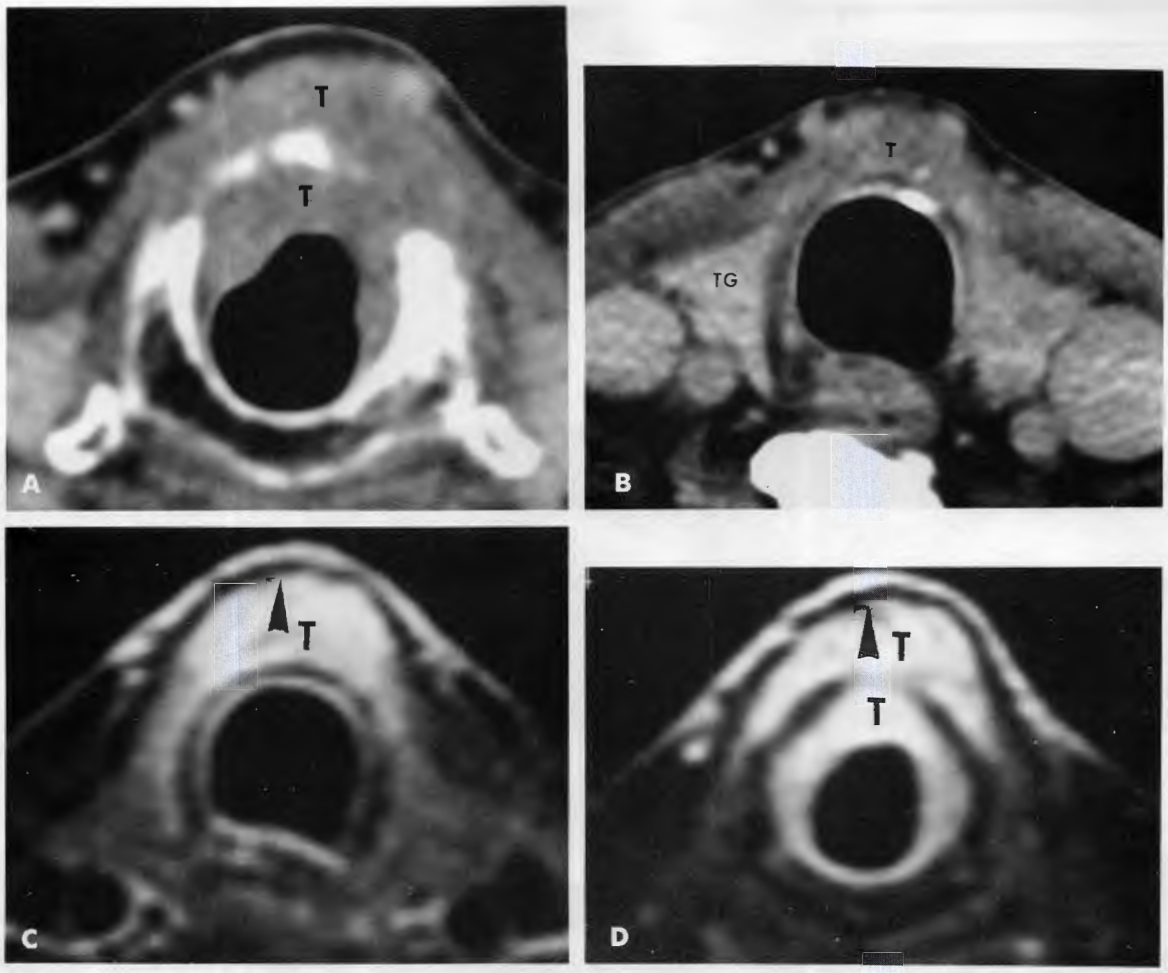

Figure 18-15. Primary subglottic cancer with no definite palpable mass in the pretracheal region, although some "fullness" was suspected. (*A*) CT scan in the low subglottic region shows tumor (T) involving three fourths of circumference. This is obviously extending through the cricothyroid membrane and into the prelaryngeal soft tissues, although it appears to be still contained by the infrahyoid strap muscles. (*B*) Section through the first tracheal ring level. Tumor is still likely present in the prelaryngeal tissues (T) approximately at the level of the isthmus of the thyroid gland (TG). (*C* and *D*) Heavily T2-weighted MRI studies corresponding with the CT level seen in *A* and *B*. The tumor T extends into the prelaryngeal and pretracheal soft tissues and displaces the infrahyoid strap muscles (*arrowheads*) anteriorly. The muscles appear as a thin dark band between the tumor and the brighter subcutaneous fat.

This case illustrates the importance of imaging findings in anticipating the lower margin of tumors for both surgical and radiotherapeutic reasons. Imaging in this patient helped avoid placement of the tracheostomy too close to the lower margin of the lesion. This case also illustrates how well MRI demonstrates extralaryngeal spread of tumor.

- Natural history of primary tumors at that site relative to cartilage invasion
- Aggressive versus nonaggressive margins
- Pattern of cartilage ossification adjacent to tumor
- Symmetry of cartilage ossification
- Sclerosis of adjacent cartilages
- Obliteration of the marrow space
- Involvement of connecting membranes
- Edema of extralaryngeal soft tissues, especially infrahyoid strap muscles (Figs. 18-16 and 18-17).

- Extralaryngeal spread. CT can distinguish extralaryngeal extension of the primary lesion from a lymph node mass and can define extension to the thyroid gland and other adjacent tissues (see Figs. 18-15 and 18-17).
- Fixed vocal cord (Fig. 18-18).
- Detection of recurrent tumor. CT is the preferred baseline examination for detection of recurrence in the neck and for study of the neopharynx or postirradiation larynx. (See section on follow-up.)
- Submucosal masses. Some patients will have squamous cell carcinoma lying entirely under intact mucosa; these primary tumors most likely begin in the laryngeal ventricle and false vocal cord and grow primarily within the paraglottic space. An enchondroma or chondrosarcoma may also present as a submucosal lesion and is readily diagnosed by CT. A well-circumscribed submucosal mass showing marked contrast enhancement may be a rare paraganglioma. Minor

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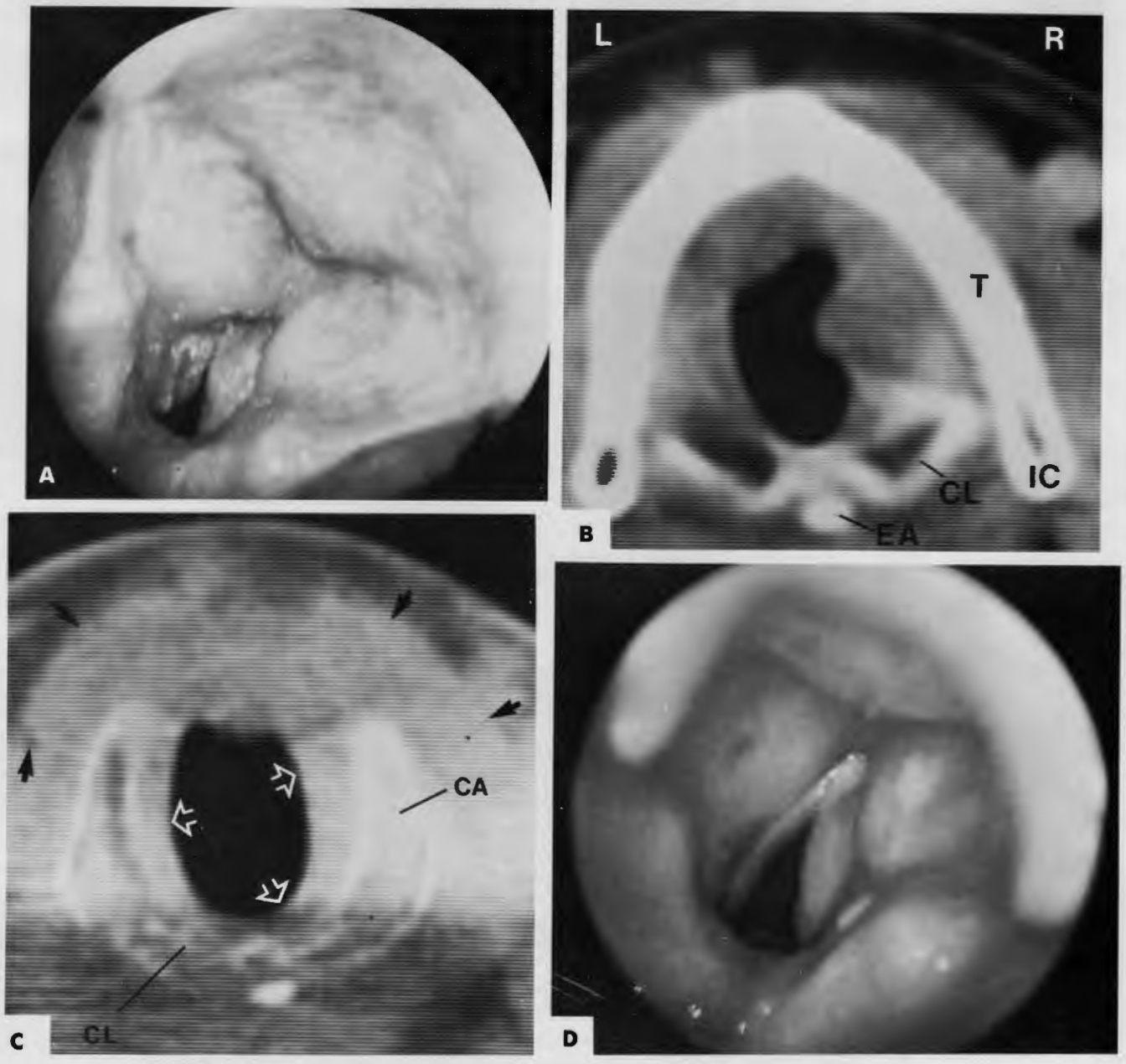

Figure 18-16. Squamous cell carcinoma of the glottic larynx in a 45-year-old man. (*A*) Appearance after biopsy, before treatment. The entire right and left vocal cords were infiltrated with tumor. The right vocal cord was fixed, and the left vocal cord was partially fixed. There was extension into the left false cord and anterior commissure. Direct laryngoscopy showed subglottic extension for at least 2 cm on both sides (T4N0). (*B*) CT scan at the transition from the true vocal cord to the infraglottic larynx. The mass extended across the midline and involved the anterior and left subglottic space. T, thryoid cartilage; IC, inferior horn of thyroid cartilage; CL, cricoid lamina; EA, vertical ridge on posterior midline of cricoid lamina, site of attachment of the longitudinal fibers of the esophagus). (*C*) CT section 5 mm below B, through the cricoid and cricothyroid membrane. There was a circumferential tumor mass (*open arrows*). There was a soft tissue mass in front of the cricoid, continuous with the subglottic mass (*black arrows*). This extralaryngeal mass was not appreciated on clinical examination. Normally there is very little soft tissue anterior to the cricothyroid membrane. CA, cricoid arches; CL, cricoid lamina. (*D*) Appearance of the larynx at 2 months. The patient died free of disease 5 years after receiving 7680 cGy over 6½ weeks, given as 120 cGy twice a day.

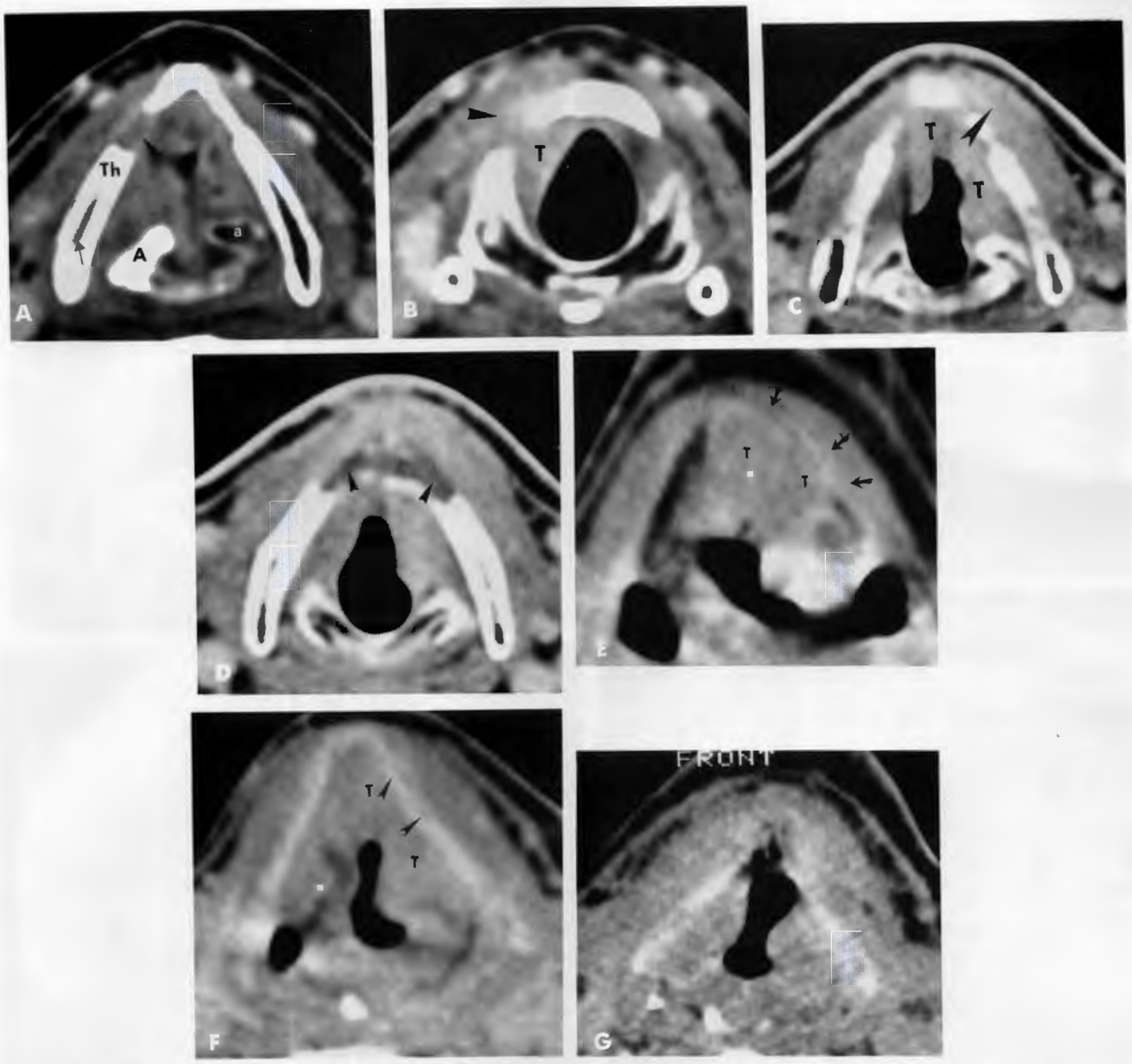

Figure 18-17. Three different patients with evidence of cartilage invasion. (*A*) The first patient had stage T3 glottic cancer. The focal defect (*arrowhead*) in the right thyroid lamina is an area of cartilage invasion that has also caused sclerosis of the right thyroid lamina (Th) compared with the left and obliteration of the fat marrow space (*arrow*) within the ossified cartilage (compared with normal marrow space on the left). The right arytenoid (A) is displaced medially and scelerotic compared with the normal left arytenoid cartilage (a). (*B*) Subglottic tumor (T) is present. There is spread to the prelaryngeal soft tissues through the cricothyroid membrane (*arrowhead*) obliterating the fat plane between the larynx and infrahyoid strap muscles (compared with normal fat plane on the left side). The cricoid cartilage is sclerotic, suggesting invasion, although this could be due to reactive sclerosis. (*C*) The second patient had a clinical stage T2 carcinoma involving the anterior commissure. Tumor involves the anterior commissure, entire left cord, and anterior portion of the right true cord (T). Irregularity of the thyroid cartilage anteriorly could be a normal variant; however, note the subtle swelling of infrahyoid strap muscles on the left side (*arrowhead*) compared with the right. (*D*) Sections at the undersurface of the true cords show tumor spreading within the marrow space of the thyroid cartilage anteriorly and bilaterally creating an almost expanded appearance within the cartilage (*arrowheads*). Also note the swelling of the infrahyoid strap muscles anterior to the larynx. There was no palpable tenderness nor mass anteriorly. Cartilage invasion and prelaryngeal spread were confirmed at surgery. (*E*) The third patient had a supraglottic carcinoma staged T2 clinically. CT revealed that this was actually a fairly high-volume lesion with tumor (T) filling the preepiglottic and paraglottic spaces and possible early spread through the thyrohyoid membrane at its attachment to the thyroid cartilage (*arrows*). (*F*) A section at the upper false cord level with tumor in the preepiglottic and paraglottic spaces (T). The left thyroid lamina was bowed inward slightly and locally indistinct with adjacent, subtle thickening of the infrahyoid strap muscles (*arrowheads*). These findings were taken as subtle evidence of cartilage invasion at the attachment of the thyrohyoid membrane. MRI was suggested to confirm early cartilage involvement and extralaryngeal spread, but the patient was too claustrophobic to be studied. (*G*) Following radiotherapy, there was evidence of localized chondronecrosis or persistent tumor at the site suspicious for cartilage invasion as seen on the pretherapy CT study (see E). Total laryngectomy revealed combined localized chondronecrosis and recurrent tumor.

Figure 18-18. A 70-year-old man had a 6-month history of progressive hoarseness. On physical examination, the right vocal cord was enlarged and fixed. There was extension to the right false cord, anterior commissure, and subglottic area. There was no palpable mass or tenderness over the thyroid cartilage. (*A*) CT scan at the level of the true vocal cords. The scan was taken during phonation. Both vocal processes rotated medially, even though the right vocal cord appeared fixed on indirect laryngoscopy. The tumor crossed the anterior commissure to involve the anterior left vocal cord. There was no ossification of the right anterior thyroid cartilage, suggesting tumor invasion. The paraglottic space was absent in this area. (*B*) Lateral xeroradiograph. There was patchy calcification of the thyroid cartilage. There was no clear-cut evidence of a soft tissue mass extending through the cartilage. If the scanning gantry follows the dashed lines, a portion of the thyroid lamina could be partially out of the scan plane, resulting in the appearance of cartilage destruction. (*C*) Anteroposterior tomogram taken with patient in quiet respiration. The internal lamina of the right thyroid cartilage was absent. The tumor mass extended subglottically and supraglotically. The cord was fixed. (*D*) Appearance at 7 months. The patient received 6750 cGy over 6 weeks, ^{60}Co. He was free of disease at 12 years. His voice was husky, although there was complete return of motion in the right vocal cord. This patient's disease was staged as T3 but was probably T4.

salivary gland tumors may also produce submucosal lesions. Submucosal mass lesions within the larynx of uncertain origin may be diagnosed. One third to one half will be laryngoceles. If there is evidence of a laryngocele (complicated or uncomplicated), a careful search for obstructing primary tumor is still mandated. Occasionally, these patients will have sustained blunt laryngeal trauma in the past that has caused some deformity of the laryngeal skeleton, resulting in a mucosal bulge.

- Vocal cord palsy. Imaging is helpful in the differential diagnosis of the patient with vocal cord paralysis and no obvious endolaryngeal lesion; the entire course of the vagus and recurrent laryngeal nerves is studied.

Direct Laryngoscopy

Direct laryngoscopy and biopsy with frozen section are usually performed with the patient under general anesthesia. A generous biopsy specimen is taken from the obvious lesion; additional biopsy specimens may be obtained from suspicious areas as well as from areas grossly involved, for purposes of staging. "Debulking" of the lesion with a CO_2 laser or a biting forceps is not recommended unless the airway is compromised by the mass; removal of "large" amounts of tumor before radiation therapy or conservation operation could theoretically reduce the chance of cure and is considered meddlesome and of no benefit to the patient. The mucosa of the margin of the vocal cord may be stripped to provide adequate tissue when the lesion is distributed superficially along the cord and is not obviously a carcinoma. The mucosa of ventricles, subglottic area, apex of the pyriform sinus, and postcricoid area must be carefully examined, since these areas are not consistently seen by any other method.

Differential Diagnosis

The differential diagnosis of laryngeal lesions includes hyperkeratosis (Fig. 18-19), papillomas, polyps, vocal nodules, fibromas, granulomas, and laryngoceles. Papillomas can involve the epiglottis or false or true cords and can extend subglottically. They generally occur in children and young adults and may persist into adulthood. They may be confused with verrucous carcinoma in adults. Four of our patients with vocal cord carcinoma were between the ages of 22 and 30 when they presented for diagnosis. There are 55 cases of laryngeal cancer reported in children 15 years of age or younger (aged 1 to 5 years in 7 cases). Carcinomas in children are often associated with papillomatosis, especially when irradiation has been used.[23] Vocal polyps and vocal nodules occur at the junction of the middle and anterior thirds of the true vocal cords. There is usually a history of voice abuse followed by hoarseness.

Granulomas of the larynx usually occur as a result of intubation and are located on the posterior third of the vocal cords, near the posterior commissure. Endoscopic removal is the definitive treatment. Contact ulcers occur over the vocal processes and are usually bilateral. They form granulation tissue around the ulcer and may be mistaken for carcinoma. Pain and hoarseness may be present.

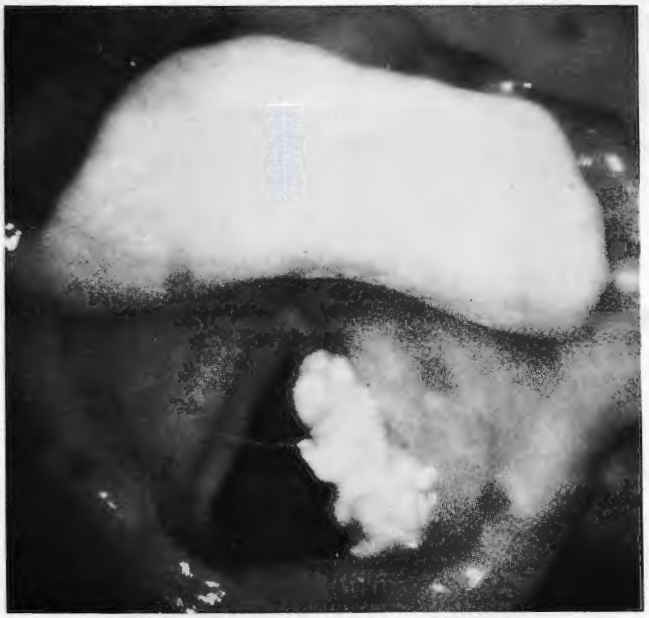

Figure 18-19. A 61-year-old woman had a history of hoarseness for 2 years. There was an obvious lesion on the right vocal cord; mobility was normal. The entire lesion was removed in pieces with biopsy forceps. The microscopic diagnosis was hyperkeratosis with mild inflammatory atypia. This lesion grossly resembles either a verrucous carcinoma or an invasive squamous cell carcinoma.

Tuberculosis of the larynx, although rare, still occurs. Generally the lesion is destructive and occurs at the posterior commissure of the glottis, the epiglottis, and the false cords. The appearance mimics cancer. Pulmonary tuberculosis is usually present.

Staging

The American Joint Committee on Cancer (AJCC) staging system for laryngeal primary cancer is listed below.[2] The AJCC and UICC are now the same. For lesions arising in the supraglottis, the sites of origin include false cords, aryepiglottic folds, suprahyoid (tip) epiglottis, infrahyoid epiglottis, and arytenoids. Only in the early T stages can one identify the specific site of origin with certainty. As the lesion enlarges, the site of origin is an educated guess based on the location of the greatest bulk of tumor. Imaging can help decide the point of origin since one can find the geometric center (epicenter of the lesion) and often recognize spread patterns typical of a particular primary site. (See Chap. 6 for N stages and Chap. 5 for total stage.)

Supraglottis

T1 Tumor limited to one subsite of supraglottis with normal vocal cord mobility

T2 Tumor invades more than one subsite of supraglottis or glottis, with normal vocal cord mobility

T3 Tumor limited to larynx with vocal cord fixation and/or invades postcricoid area, medial wall of pyriform sinus, or preepiglottic tissues
T4 Tumor invades through thyroid cartilage, and/or extends to other tissues beyond the larynx (eg, to oropharynx, soft tissues of neck)

Glottis

T1 Tumor limited to vocal cords (may involve anterior [or posterior] commissures) with normal mobility
T1a Tumor limited to one vocal cord
T1b Tumor involves both vocal cords
T2 Tumor extends to supraglottis and/or subglottis, with impaired vocal cord mobility
T3 Tumor limited to the larynx with vocal cord fixation
T4 Tumor invades through thyroid cartilage and/or extends to other tissues beyond the larynx (eg, oropharynx, soft tissues of neck)

Subglottis

T1 Tumor limited to the subglottis
T2 Tumor extends to vocal cords with normal or impaired mobility
T3 Tumor limited to larynx with vocal cord fixation
T4 Tumor invades through cricoid or thyroid cartilage and/or extends to other tissues beyond the larynx (eg, oropharynx, soft tissues of neck)

The lower boundary of the glottis is considered to be the horizontal plane 1 cm below the apex of the ventricle according to the AJCC. We prefer to consider the junction 5 mm below the free margin of the vocal cord.

Extension below the cricotracheal level is considered tracheal extension. Caution is advised in interpretation of cartilage invasion by CT or MRI scan.

According to the AJCC, T1 lesions of the glottis include involvement of the posterior commissure. The posterior commissure is the mucous membrane covering the posterior cricoid cartilage. A glottic cancer would first have to involve the arytenoid to reach the posterior commissure and would become a T2 before ever reaching the posterior commissure. Only one primary carcinoma arising from the posterior commissure has been seen. These rare lesions should probably be considered subglottic carcinomas rather than glottic lesions.

TREATMENT

Vocal Cord Carcinoma

Selection of Treatment Modality

The goal is cure with the best functional result and the least risk of a serious complication. For purposes of treatment planning, patients may be considered to be in either an early group or a late group. The early group may be treated initially by radiation therapy or in selected cases by partial laryngectomy. The late group may be treated by irradiation with laryngectomy reserved for failure or with total laryngectomy with or without radiation therapy.

DYSPLASIA, HYPERKERATOSIS, LEUKOPLAKIA. Complete stripping of the mucosa of the cord is often curative for lesions classified as leukoplakia, hyperkeratosis, or dysplasia. Careful observation is essential, since regrowth of the lesions often occurs. Although repeated stripping with or without the use of a laser may seem a satisfactory plan of management, the cords may become thickened and the voice harsh, and it becomes increasingly difficult to tell whether invasive tumor is present. Irradiation may be recommended when there are repeated recurrences at short intervals.

CARCINOMA IN SITU. Lesions diagnosed as carcinoma in situ may sometimes be controlled by stripping the cord. It is difficult, however, to exclude the possibility of microinvasion on these specimens. (See section on pathology.) Recurrence is frequent, and the cord may become thickened and the voice hoarse with repeated stripping.

Irradiation is recommended when there is rapid recurrence or after multiple recurrences of carcinoma in situ. Earlier use of irradiation means a better chance of preserving a good voice.

A few of the cases treated as carcinoma in situ have obvious lesions that probably contain invasive carcinoma. We have sometimes proceeded with radiation therapy rather than put the patient through a repeat biopsy.

EARLY VOCAL CORD CARCINOMA. In most centers, irradiation is the initial treatment prescribed for early lesions, with operation reserved for salvage of irradiation failures. While hemilaryngectomy or cordectomy will produce comparable cure rates for selected T1 and T2 vocal cord lesions, irradiation is generally the preferred initial therapy. The major advantages of irradiation compared with laser excision, cordectomy, or hemilaryngectomy are that the selection criteria are less restrictive, the voice is likely to be better, a major operation is avoided, the complication rate is less, and the rates of local control and survival are comparable. The voice after hemilaryngectomy remains hoarse; we tell the patient that the voice will be "as hoarse as it is now or even worse." The voice after successful irradiation is usually better than before therapy, but occasional cases are seen in which there is no improvement or, uncommonly, a worsening. Hemilaryngectomy finds its major use as a salvage operation in suitable cases after irradiation failure. Even if the patient has a local recurrence after a salvage hemilaryngectomy, there is a third chance with total laryngectomy, which may still be successful.[6] The complications reported for cordectomy and hemilaryngectomy are discussed in the complications section.

Verrucous lesions have the reputation of being unresponsive to irradiation and, in some instances, losing their verrucous nature to convert into invasive, often anaplastic, metastasizing lesions after unsuccessful irradiation. Hemilaryngectomy is recommended for early verrucous carcinoma of the glottis, but radiation therapy is recommended if the alternative is total laryngectomy. The patient must be advised of the added risks when radiation therapy is used for verrucous carcinoma. Hemilaryngectomy is also used in patients who have had prior head and neck irradiation that prohibits further irradiation.

MODERATELY ADVANCED VOCAL CORD CARCINOMA. Fixed-cord lesions (T3) may be subdivided into relatively early, favorable lesions suitable for voice preservation therapy and unfavorable lesions, the latter usually having extensive bilateral disease with a compromised airway. The favorable T3 lesion has tumor confined mainly to one side of the larynx; the patient has a good airway, and the area is reasonably easy to examine. The patient with a favorable lesion is advised of the alternatives of radiation therapy with surgical salvage and immediate total laryngectomy. Occasionally, a patient will have what appears to be a favorable T3 lesion and the radiologist hints at possible minimal cartilage invasion; we have still offered radiation therapy to these patients.[52] The local control rate with voice preservation with radiation therapy is 50% to 70%, and 50% to 70% of failures are cured. The patient is advised that there may be a reduction (5% to 10%) in the 5-year survival rate compared with immediate total laryngectomy and that should laryngectomy be required, the risk of complications is greater. The patient must be willing to return for close follow-up and understand that total laryngectomy may be recommended purely on clinical grounds without biopsy-proven recurrence. Few chose total laryngectomy when presented with these options by the surgeon and radiation oncologist.

An evolving strategy for patients normally selected for laryngectomy is to start treatment with chemotherapy and select those who have a good response to chemotherapy for trial of radiation therapy with laryngectomy reserved for persistent disease. Preliminary results from the Veterans Administration Laryngeal Cancer Study Group[12a,35,88a] and Memorial Sloan-Kettering Hospital[66] are promising.

The major difficulty in the use of irradiation for the more advanced lesions is to distinguish between radiation edema and local recurrence during follow-up examinations. Extended hemilaryngectomy has been used with success by a few surgeons in the treatment of well-lateralized fixed-cord lesions. A permanent tracheostomy may be required because a portion of the cricoid is resected, but a useful voice may be retained.[64]

ADVANCED VOCAL CORD CARCINOMA. The mainstay of treatment in most centers for extensive T3 and nearly all T4 lesions is total laryngectomy, with or without postoperative irradiation; the addition of neck dissection is individualized for each case (see Chap. 6). If the neck is clinically negative before the operation and postoperative irradiation is definitely planned, neck dissection is not done and irradiation is used to treat both sides of the neck; if postoperative irradiation is not definitely planned, an elective neck dissection is done. The most frequent sites of local failure after total laryngectomy are around the tracheal stoma, in the base of the tongue, and in the neck lymph nodes.

Radical irradiation is prescribed for the patient with an advanced T3 or T4 lesion who refuses total laryngectomy or is medically unsuitable for a major operation. A few patients in this category will be cured and maintain a useful voice.

Surgical Treatment

Stripping of the vocal cord implies transoral removal of the mucosa. The operating microscope is used by the surgeon in total stripping of the mucosa.

Thyrotomy with cordectomy is an excision of the vocal cord. Its use is usually confined to small lesions of the middle third of the cord. Cordectomy is generally reserved for that uncommon situation in which there is a postirradiation recurrence limited to the middle third of the cord with normal mobility. After cordectomy, a pseudocord is formed and the patient has a useful, if somewhat harsh, voice. A portion of the adjacent thyroid cartilage may be removed with the cord.

Laser excision of vocal cord carcinoma has been advocated by some surgeons with the principal advantages of less cost and less treatment time. Although these are legitimate goals, the number of cases suitable for the use of a CO_2 laser is limited. Lesions limited to the middle third of the true cord (primary or recurrent) can be easily treated with the laser. Larger lesions involving the entire cord, those involving the anterior commissure, and those with subglottic and supraglottic extension are not suitable for laser excision. The voice will not be normal since a section of vocal cord is resected.

Hemilaryngectomy is a partial, "vertical" laryngectomy that allows removal of limited cord lesions with preservation of voice (Fig. 18-20). One entire cord plus up to one third of the opposite cord is the maximum involvement suitable for the operation in men; women have a smaller larynx, and usually only one vocal cord and a few millimeters of the opposite cord may be removed without compromising the airway. Partial fixation of one cord is not a contraindication to hemilaryngectomy, but only a few surgeons have attempted hemilaryngectomy for selected fixed-cord lesions. The maximum subglottic extension allowable is 8 to 9 mm anteriorly and 5 mm posteriorly, to preserve the integrity of the cricoid. Tumor extension to the epiglottis, false cord, or both arytenoids is a contraindication to hemilaryngectomy. Less than 5% of hemilaryngectomies are converted to total laryngectomies at the time of operation in properly selected cases. The last surgical alternative is total laryngectomy with or without neck dissection. The entire larynx is removed, and the pharynx is reconstituted. A permanent tracheostomy is required (see Chap. 19).

Irradiation Technique

Irradiation for early vocal cord cancer (T1 to T2) is delivered by small portals covering only the primary lesion. The incidence of lymph node involvement is so small that elective irradiation of lymph nodes is not recommended. Minimum radiation portals extend from the mid-thyroid notch superiorly to the inferior border of the cricoid; the posterior border depends on posterior extension of the tumor (Fig. 18-21). The field size ranges from 4×4 to 5×5 cm and is occasionally 6×6 cm for a large T2 lesion. Portals larger than this increase the risk of edema without increasing the cure rate. Since the portals are small and the skin of the neck is mobile, it is our practice to have the physician check the portal on the treatment table each day by palpation of the anatomic landmarks.

Either cobalt-60 (^{60}Co) or 4-MV photons is recommended. There are limited data for 6-MV photons, but one Japanese series of T1 glottic carcinomas reported an 81% local control rate for 27 patients with anterior commissure invasion compared with 91% (127 patients) without anterior commissure invasion ($P = .06$).[1]

The current dose scheme used at the University of Florida is shown in Table 18-4. (See Chap. 12 for a discus-

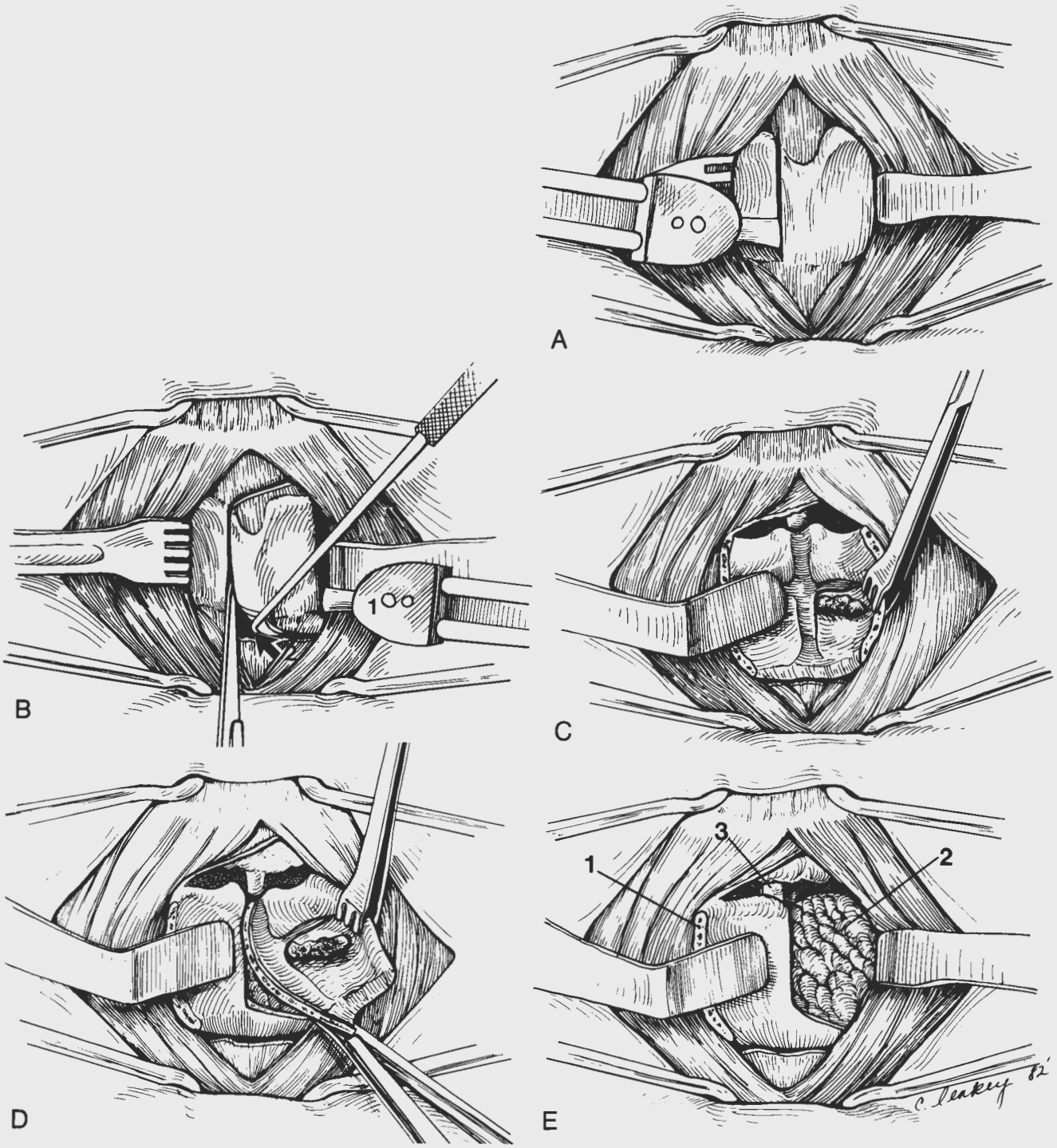

Figure 18-20. Hemilaryngectomy for carcinoma of the left vocal cord with extension to the anterior commissure. (*A*) Strap muscles are retracted, exposing the thyroid cartilage. Perichondrium on the left is preserved. A saw cut is made just to the right of the midline. (*B*) A saw cut is made through the posterior edge of the thyroid cartilage, leaving 2 to 3 mm of cartilage posteriorly (1). The larynx is then entered anteriorly through the cricothyroid membrane (2). The lesion can then be viewed through a 1-cm exposure. A knife cut through the mucosa to the right of the midline is made under direct vision, and the incision is joined superiorly and inferiorly to the posterior cut. (*C*) The thyroid laminae are retracted, and the lesion is exposed. The posterior extent is now clearly visible. (*D*) The posterior mucosal cut is made along the line of the posterior cartilage cut. The final cut may include the arytenoid if it is involved. (*E*) Surgical defect after the specimen has been removed. Closure is completed by suturing the perichondrium from the left side to the perichondrium and thyroid cartilage on the right side (1). 2, mucosa of the pharyngeal wall; 3, nasogastric tube.

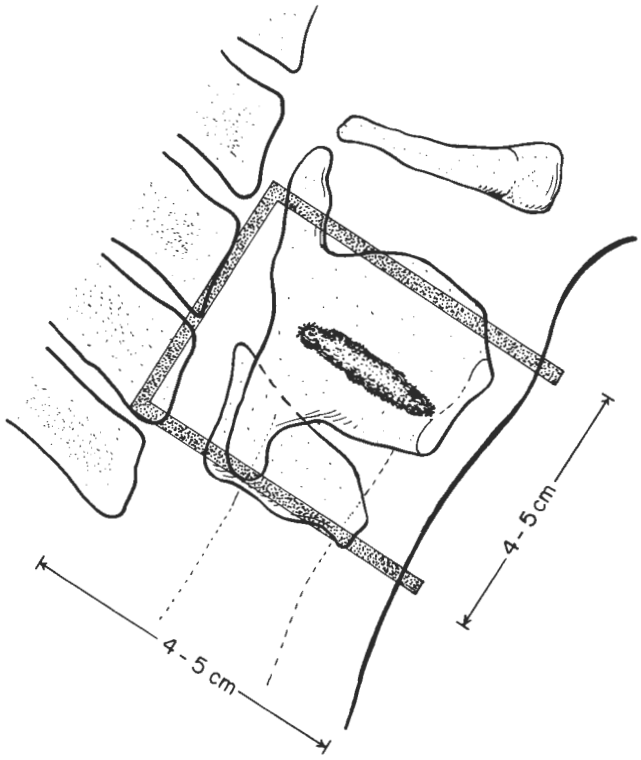

Figure 18-21. Treatment portal for early vocal cord carcinoma. The top border is adjusted according to the lesion. The bottom of the thyroid notch is the landmark for the very early lesions and the top of the notch for larger lesions or those with minimal supraglottic extension. The posterior border is the back edge of the thyroid cartilage if the lesion is confined to the anterior two thirds of the vocal cord; if the posterior one third of the vocal cord is involved, then the posterior border is placed 1.0 to 1.5 cm behind the cartilage. The transition from the undersurface of the vocal cord to the subglottic larynx begins at the level of the thyrocricoid membrane. The inferior border is placed at the bottom of the cricoid cartilage when there is no subglottic extension.

sion of dose.) All T2 and T3 lesions are managed with 120 cGy twice-daily fractionation and a 6-hour interval between fractions; the total dose should not exceed 7680 cGy.

Mendenhall and associates reviewed the impact of total dose and dose per fraction on local control and complications.[47] The findings are summarized in Table 18-5. A time–dose response could not be shown for T1a lesions less than 5 mm, T1a lesions greater than 15 mm, and T1b lesions, and they are excluded from the table. There is a reduction in local control as the dose per fraction is decreased (ie, longer overall time), even though the total doses remain the same or are increased. Use of 180 cGy per fraction is reported to show a significant decrease in local control for T1 and T2 lesions.[70] Hypofractionation techniques produce a reduced control rate or an increased risk for a complication.[28,88]

Teshima and coworkers compared portal sizes, 5×5 cm versus 6×6 cm, in a randomized trial of 87 T1 glottic carcinomas treated with 4 MV. There was no difference in the local control rate. Acute mucosal reaction and arytenoid edema were more common in the 6×6 cm group.[80]

Three techniques for T1–T2 lesions treated by ^{60}Co are compared in Figure 18-22. A single lateral ^{60}Co portal was used in the past when only one cord was involved; it delivered a maximum dose to normal tissue that was 10% to 12% greater than the tumor dose and produced subcutaneous changes. (See section on skin and subcutaneous tissues in Chap. 13.) The three-field arrangement reduces the high-dose volume. The anterior portal is usually 3×3 to 4×4 cm and centers the high dose to the tumor. The weighting of the portals and the use of wedges or compensators are individualized to each case. The tumor dose is specified to the isodose that encompasses the gross disease.

Primary portals for irradiation of T3 and T4 lesions also include as a minimum the jugulodigastric, middle jugular, and Delphian lymph nodes (Fig. 18-23).[62] The inferior jugular and low lateral paratracheal lymph nodes are included, usually in a separate low neck portal. When the most inferior extension of the primary lesion is shielded on the lateral portals by the shoulders, the lateral portals may be angled inferiorly and the shoulders pulled down by grasping a rope wrapped around the shoes. An alternative is the technique outlined in Chapter 21. The size of the primary portals is reduced after 4600 cGy (200 cGy per fraction). If the neck is clinically negative, the reduced portals cover only the primary lesion, and the dose per fraction is increased to 225 cGy, one fraction per day. The reduced-portal arrangement is similar to the one described for T1 and T2 lesions. The final dose is 6850 to 7075 cGy in 33 to 34 fractions. Twice-a-day fractionation (120 cGy twice-a-day) to 7440 to 7680 cGy over 6½ weeks has been used since 1978 for T3 and T4 lesions, and the functional result is generally good. (See Color Fig. 1*B* and *C* in Chap. 3.)

Management of Recurrence

Most recurrences appear within 2 years, but late recurrences are reported after 5 years.[18] The risk of meta-

TABLE 18-4. Radiation Treatment Dose Guidelines for Vocal Cord Carcinoma at the University of Florida (January 1991)

		Fraction Per Day	Schedule*
T1	Minimal tumor	1	5625 cGy in 25 fractions over 5 weeks
T1	>Minimal tumor	1	6300 cGy in 28 fractions over 5½ weeks
T2	All cases	1	6300 cGy in 28 fractions over 5½ weeks
		2	7440 cGy in 62 fractions over 6 weeks
T3	All cases	2	7440 cGy in 62 fractions over 6 weeks
T4	All cases	2	7680 cGy in 64 fractions over 6½ weeks

* The tumor dose is specified to the isodose that encompasses the gross disease.

TABLE 18-5. Vocal Cord Carcinoma: Local Control as a Function of Dose Per Fraction and Total Dose (No. Controlled/No. Treated)

Stage	Total Dose (cGy)	Dose Per Fraction (cGy)	Local Control
T1a-C (5-15 mm)	6100–6500	225	32/32 (100%)
	6100–6700	200–220	22/25 (88%)
	5600–5700	225–230	16/18 (89%)
T2a-HL	6100–6500	225	15/16 (94%)
	6100–6500	215–220	5/6
	6500–7000	180–200	2/4
T2a-TL	6100–6500	225	17/18 (94%)
	6100–6500	215–220	2/5
	6500–7000	180–190	2/6
T2b	6100–6800	220–225	19/25 (76%)
	6100–7000	205–215	5/8
	6100–7000	180–200	6/9

(Mendenhall WM, Parsons JT, Million RR, Fletcher GH. T1–T2 squamous cell carcinoma of the glottic larynx treated with radiation therapy: relationship of dose-fractionation factors to local control and complications. Int J Radiat Oncol Biol Phys 1988;15:1271)

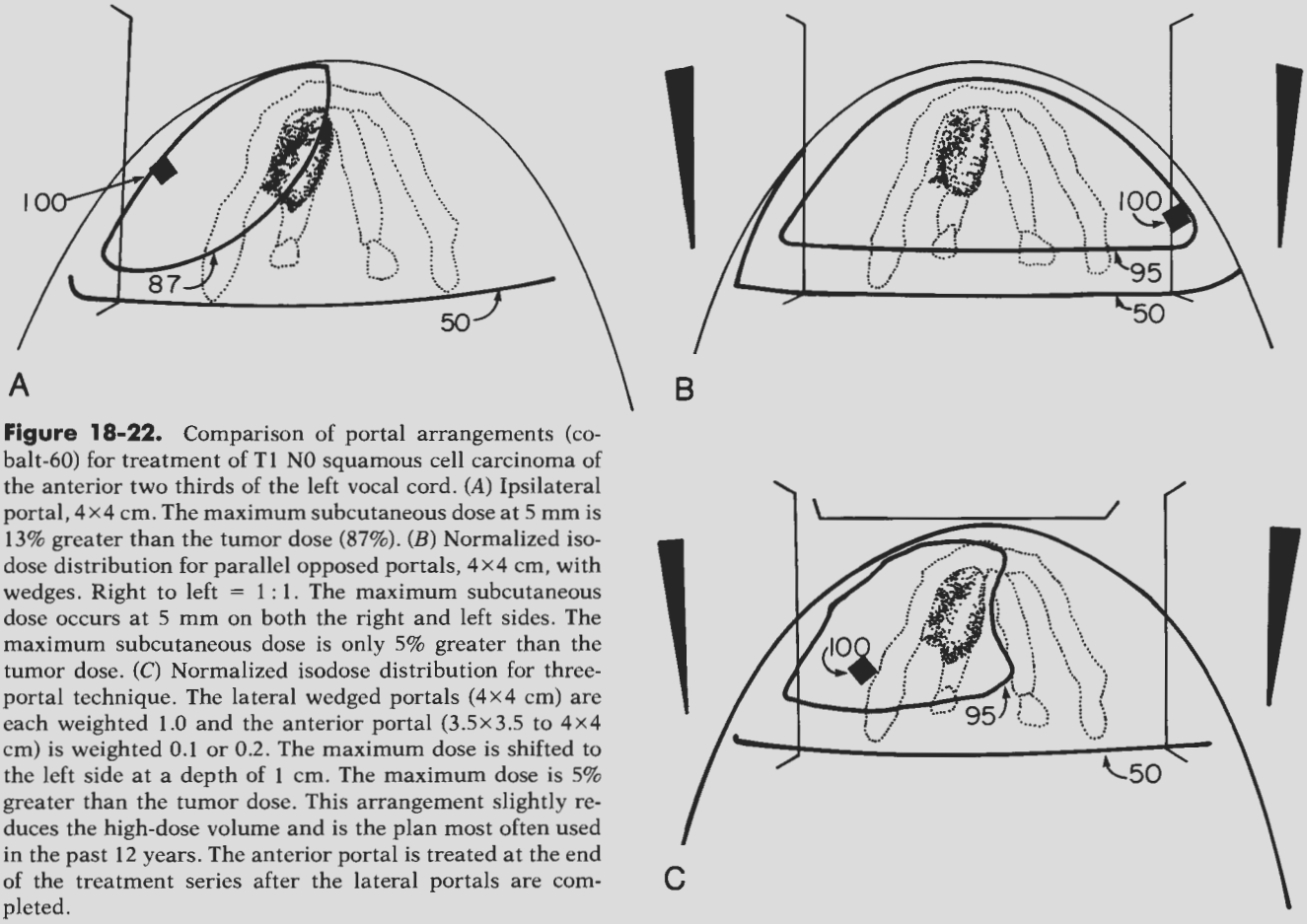

Figure 18-22. Comparison of portal arrangements (cobalt-60) for treatment of T1 N0 squamous cell carcinoma of the anterior two thirds of the left vocal cord. (*A*) Ipsilateral portal, 4×4 cm. The maximum subcutaneous dose at 5 mm is 13% greater than the tumor dose (87%). (*B*) Normalized isodose distribution for parallel opposed portals, 4×4 cm, with wedges. Right to left = 1:1. The maximum subcutaneous dose occurs at 5 mm on both the right and left sides. The maximum subcutaneous dose is only 5% greater than the tumor dose. (*C*) Normalized isodose distribution for three-portal technique. The lateral wedged portals (4×4 cm) are each weighted 1.0 and the anterior portal (3.5×3.5 to 4×4 cm) is weighted 0.1 or 0.2. The maximum dose is shifted to the left side at a depth of 1 cm. The maximum dose is 5% greater than the tumor dose. This arrangement slightly reduces the high-dose volume and is the plan most often used in the past 12 years. The anterior portal is treated at the end of the treatment series after the lateral portals are completed.

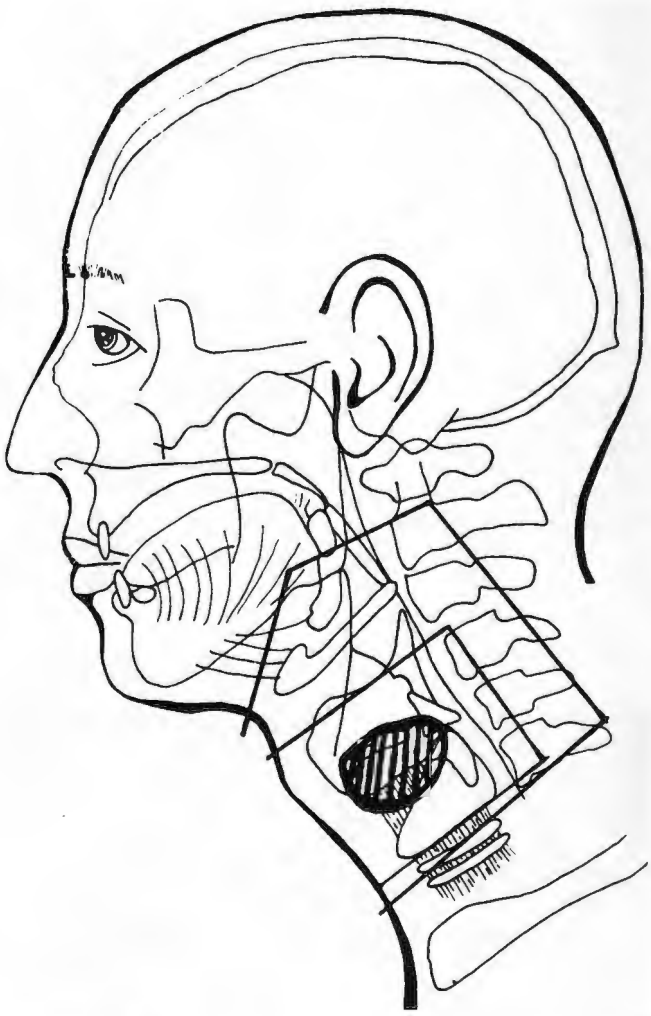

Figure 18-23. Portals for T3–T4 lesions: The initial portal includes the jugulodigastric and midjugular lymph nodes. In the N0 patient, the highest jugular lymph nodes near the base of the skull are at little risk of involvement. To ensure adequate coverage of the midjugular lymph nodes, it is necessary to include the spinal cord in the treatment volume. The placement of the inferior border depends on the presence and degree of subglottic extension as determined by direct laryngoscopy and computed tomography and is commonly 1.0 to 2.0 cm below the inferior border of the cricoid cartilage; this line is slanted to facilitate matching with the anterior low neck portal. Anteriorly, the beam is allowed to "fall off" over the skin and subcutaneous tissues. The entire preepiglottic space is included within the initial treatment volume. (Parsons JT, Mendenhall WM, Mancuso AA, Cassisi NJ, Stringer SP, Million RR. Twice-a-day radiotherapy for T3 squamous cell carcinoma of the glottic larynx. Head Neck 1989;11:124)

static disease in lymph nodes increases with local recurrence, and the lymph nodes should be either electively treated or watched closely.

RECURRENCE AFTER RADIATION THERAPY. With careful follow-up, recurrence is sometimes detected before the patient notices return of hoarseness. There is often minimal lymphedema for 1 or 2 months after radiation therapy, which usually subsides or stabilizes. An increase in edema, particularly if associated with hoarseness or pain, is suggestive of recurrence, even if no obvious tumor is seen. Fixation of a previously mobile vocal cord usually implies local recurrence, but we have observed five patients who developed a fixed cord with an otherwise normal-appearing larynx and who have not shown evidence of recurrence. A paralyzed left vocal cord should also suggest the possibility of lung cancer.

It may be difficult to diagnose recurrence when the tumor is submucosal (Fig. 18-24). Generous, deep biopsies are required. If recurrence is strongly suggested, laryngectomy may rarely be advised without biopsy evidence of recurrence.

Irradiation failures may be treated by cordectomy, hemilaryngectomy, or total laryngectomy. An example of a patient salvaged by hemilaryngectomy after a radiation therapy failure is shown in Figure 18-25. Biller and coworkers reported a 78% salvage rate by hemilaryngec-

Figure 18-24. Carcinoma of the vocal cord, recurring 3 years after radiation therapy (coronal section at mid cord level). The cord was fixed at the time of surgery. There was no gross evidence of disease in the specimen; the mucosa was smooth and intact. There was submucosal tumor replacing the vocal muscle and growing through the thryocricoid space. There was subglottic extension to a level just below the top of the cricoid cartilage. C, cricoid cartilage; T, thyroid cartilage; FC, false cord; E, epiglottis. (Courtesy of A.W. P. van Nostrand, Toronto General Hospital, Ontario, Canada)

Figure 18-25. A 57-year-old man had moderately well-differentiated squamous cell carcinoma of the left vocal cord with minimal extension to the false cord (T2N0). The patient received 7000 cGy in 35 fractions over 7 weeks (^{60}Co). Edema of the larynx and sore throat with ear pain developed at 6 months; results of biopsies were negative. Intermittent sore throat, hoarseness, and edema continued until recurrence became obvious on the left vocal cord at 15 months. A left vertical hemilaryngectomy was done; the arytenoid was spared. The tumor margins were free. This photograph was taken 6 years after left hemilaryngectomy. The patient's voice was hoarse. He was free of disease 8 years after hemilaryngectomy.

tomy for 18 selected patients in whom irradiation failed.[6] Total laryngectomy was eventually required in two patients. Only two patients died of cancer. These investigators recommended the following four guidelines for the use of salvage hemilaryngectomy: (1) contralateral vocal cord normal, (2) arytenoid not involved, (3) subglottic extension not exceeding 5 mm, and (4) vocal cord not fixed.

Wang and McIntyre[84a] analyzed the Massachusetts General Hospital experience for reirradiation of the larynx when new or recurrent cancer develops in the larynx. Nineteen patients were irradiated initially for T1 or T2 glottic carcinoma and one for a T1 supraglottic carcinoma. Fourteen patients were reirradiated for T1 or T2 glottic lesions, four for early supraglottic lesions, one for a subglottic lesion, and one for a hypopharyngeal lesion. The disease was locally controlled in 13 patients; five patients had persistent disease, and the status was unknown in two patients. The 5-year actuarial control rate was 61% and the 5-year survival rate was 93%, including five patients sucessfully salvaged by total laryngectomy. The functional result was satisfactory in the majority of survivors. There was mild fibrosis but not severe necrosis, in spite of administration of the second full dose of irradiation.

RECURRENCE AFTER SURGERY. Salvage by radiation therapy for recurrences or new tumors that appear after hemilaryngectomy is about 50%. Lee and coworkers reported seven successes in 12 patients; one lesion was subsequently controlled by total laryngectomy.[41] Total laryngectomy will salvage almost all hemilaryngectomy failures not suitable for radiation therapy.

Radiation therapy will occasionally cure a patient with recurrence in the neck or stoma after total laryngectomy. Surgical resection should be considered for stoma recurrence.[24]

Supraglottic Larynx Carcinoma

Selection of Treatment Modality

For purposes of treatment planning, patients may be considered to be in either an early or favorable group suitable for radiation therapy or supraglottic laryngectomy or an unfavorable group often requiring total laryngectomy. Neck nodes are commonly involved and influence the overall treatment plan.

EARLY SUPRAGLOTTIC LESIONS. Treatment of the primary lesion for the early group is either by external-beam irradiation or supraglottic laryngectomy. Total laryngectomy is reserved for those who fail the initial treatment and would rarely be indicated as the initial treatment. Irradiation and supraglottic laryngectomy are both highly successful modes of therapy for the early lesions, and for this reason it is seldom necessary to combine radiation therapy and surgery for initial management of the primary lesion; however, combined treatment may be indicated to control the neck disease. The following paragraphs outline our guidelines for selection of supraglottic laryngectomy or radiation therapy.

The large, bulky infiltrative lesions are often selected for supraglottic laryngectomy; about one half of these cases receive postoperative irradiation.

About one half of the patients seen in our clinic whose lesions are technically suitable for treatment by a supraglottic laryngectomy are not suitable for medical reasons (eg, inadequate pulmonary status or other major medical problems), and these patients are managed by radiation therapy (Fig. 18-26).

Analysis of local control by anatomic subsite within the supraglottic larynx shows no obvious differences in local control by radiation therapy when comparing similar stages. (See Table 18-17 in section on results of treatment.) Lesions extending to the vocal cords and subglottic area are not suitable for supraglottic laryngectomy, but they may be managed by radiation therapy in favorable cases (Fig. 18-27). Invasion of the preepiglottic space or the epiglottis is not a contraindication to supraglottic laryngectomy or radiation therapy. Freeman and associates analyzed the influence of extent of preepiglottic space invasion on the likelihood of local control by radiation therapy. Tumor volumes were measured from CT scans for 31 evaluable patients. Local control for T3 lesions as a function of percent involvement of the preepiglottic space is presented in Table 18-6[21]; slightly better control was seen with less than 25% involvement. There was a significant decrease in local control for tumor volume greater than 6 cm^3 (Table 18-7).[21]

Mendenhall and associates reviewed 129 patients with supraglottic cancer managed by initial radiation therapy to the primary lesion and analyzed local control as to whether the lesions were anatomically suitable or not suitable for supraglottic laryngectomy; there was no significant difference in the two groups (Table 18-8). Patients medically suitable for supraglottic laryngectomy were compared with the medically unsuitable, and there was no difference in local control (see Table 18-8).[49]

(text continues on page 470)

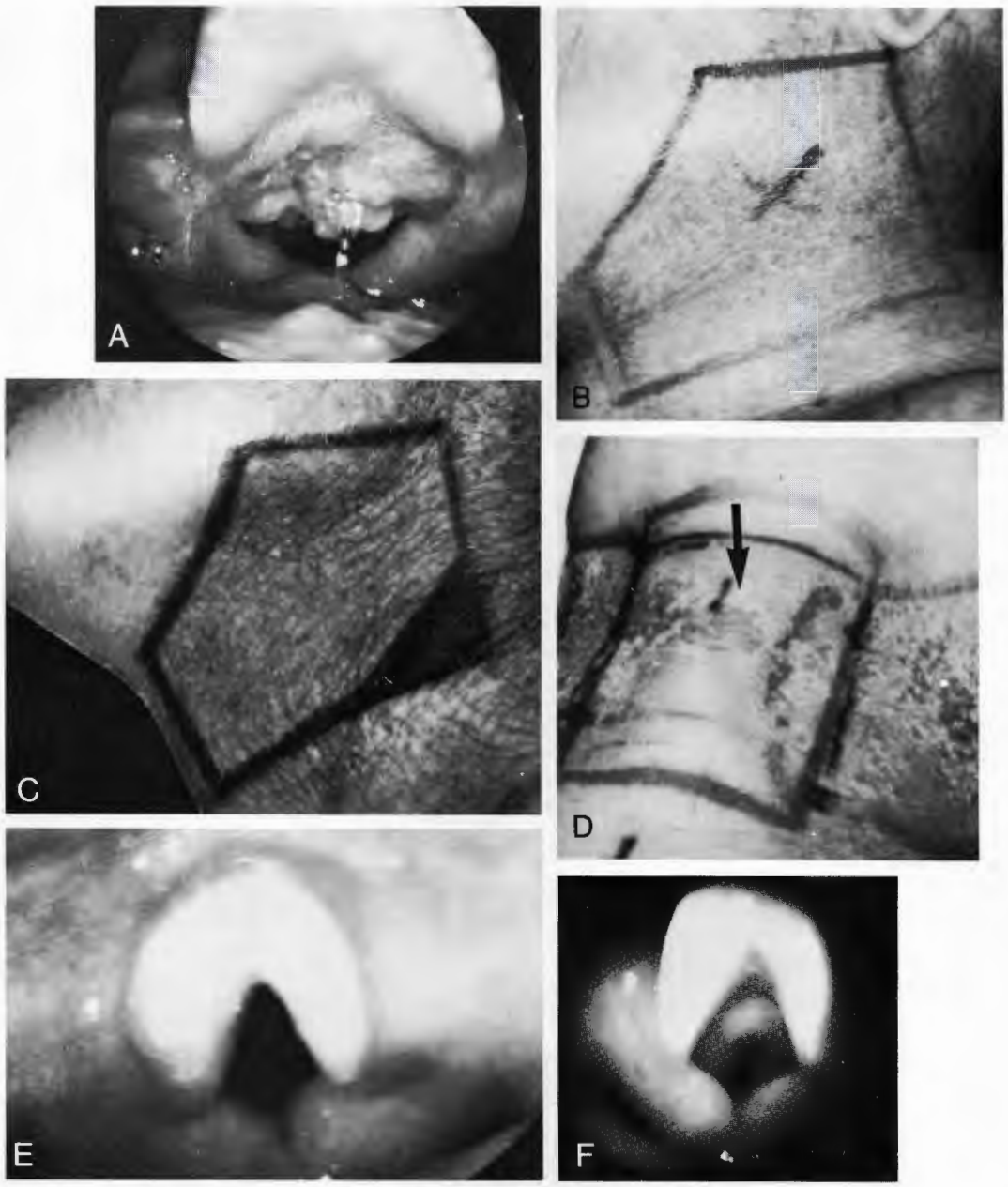

Figure 18-26. A 64-year-old man had a 6-month history of dysphagia, hoarseness, and cough productive of mucus that was sometimes mixed with blood. His past history included coronary artery disease, hypertension, pulmonary emphysema, and adenocarcinoma of the prostate. (For color photographs see Plate 5*A* and *B* in Chap. 3.) (*A*) Exophytic, bulky squamous cell carcinoma of the infrahyoid epiglottis with minimal involvement of the false cords and aryepiglottic folds (T2N0). The anterior commissure and true vocal cords were free of disease. Irradiation was recommended since the patient was medically unsuitable for supraglottic laryngectomy and was a borderline risk for total laryngectomy. He received 7000 cGy over 7 weeks (^{60}Co). (*B*) Treatment plan was with parallel opposed lateral portals, 4500 cGy over 5 weeks, ^{60}Co. (*C*) Parallel opposed reduced lateral portals, 2000 cGy over 2 weeks, ^{60}Co. (*D*) Anteroposterior portal, 500 cGy in three fractions, ^{60}Co. The lower neck was not treated. Note small area of skin change (*arrow*) in the anterior skin, even though an attempt was made to spare this strip of tissue. (*E*) Appearance 6 months after radiation therapy. The patient had a 2-week history of sore throat, hoarseness, and dysphagia. On indirect examination, there was 2+ lymphedema of the epiglottis and arytenoids but the vocal cords appeared normal. There was studding of the mucous membrane consistent with candidiasis. The edema gradually resolved over the next 6 months. (*F*) At 2 years there was persistent 1+ lymphedema but the airway was adequate. There was no evidence of disease at 5 years and minimal edema.

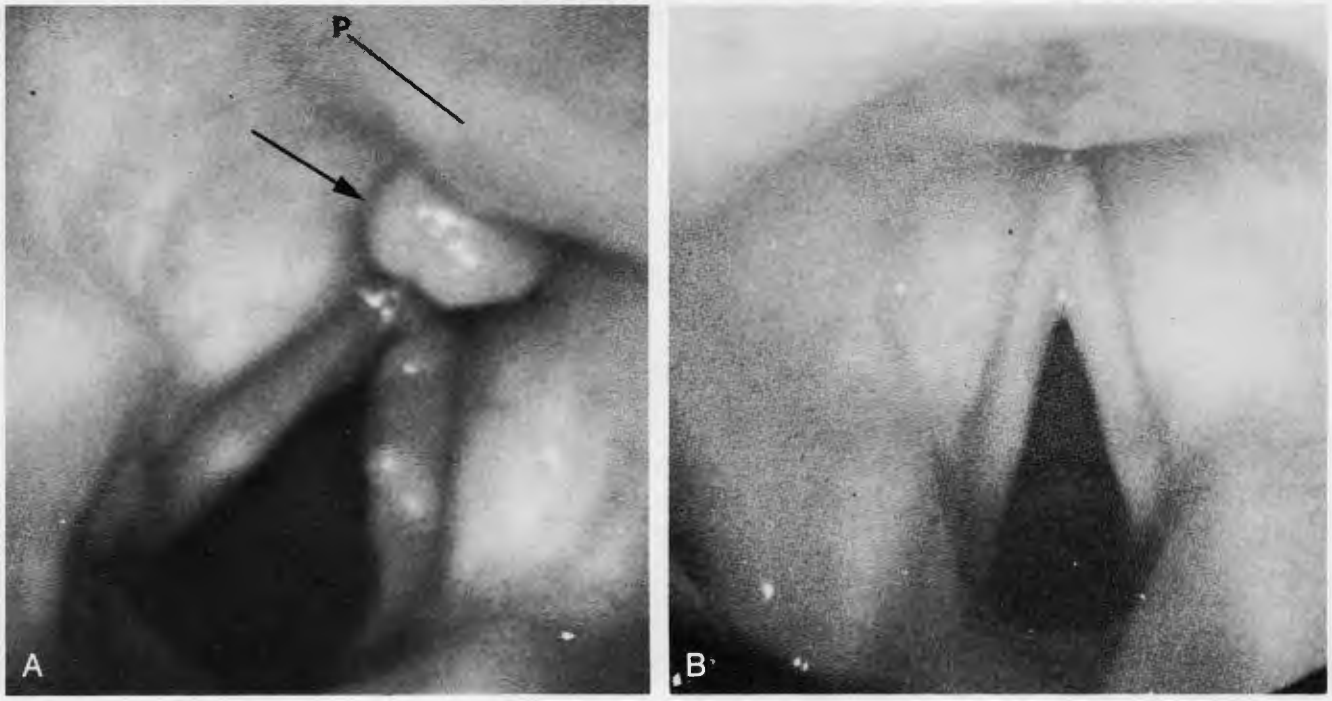

Figure 18-27. (*A*) Squamous cell carcinoma of the epiglottis (*arrow*) with extension to the left false cord. The right vocal cord appeared to be involved, but the biopsy result was negative. There was a 3-mm subglottic extension at the anterior commissure on direct laryngoscopy. The vocal cords were mobile (T2N0). Treatment was 6300 cGy in 28 fractions over 5 weeks, ^{60}Co. The lymph nodes were *not* electively irradiated. P, petiole of epiglottis. (*B*) Appearance of larynx at 8 months. A 2.5-cm subdigastric lymph node appeared at 18 months. Radical neck dissection disclosed one lymph node that contained poorly differentiated carcinoma with extracapsular extension. Irradiation was added to the left upper neck (6000 cGy over 5 weeks, 10-MeV electrons). Patient was free of disease 11 years following irradiation of the larynx.

TABLE 18-6. Supraglottic Carcinoma: Local Control as an Estimated Percent of Preepiglottic Space Involvement on CT Scan

Preepiglottic Space Involvement	Local Control After Radiation Therapy Alone
None	3/4
<25%	6/8
25%–75%	2/4
>75%	4/6

For <25% preepiglottic space involvement (9/12, 75%) vs. ≥25% preepiglottic space involvement (6/10, 60%, P = .384).
(Freeman DE, Mancuso AA, Parsons JT, Mendenhall WM, Million RR. Irradiation alone for supraglottic larynx carcinoma: can CT findings predict treatment results? Int J Radiat Oncol Biol Phys 1990;19:488)

TABLE 18-7. Supraglottic Carcinoma: Local Control as a Function of Tumor Volume (31 Patients)

	Local Control by Tumor Volume	
Stage	<6 cm²	≥6 cm²
T1	3/3	—
T2	3/4	0/1
T3	9/11 (82%)	6/11 (55%)
T4	—	0/1
Total*	15/18 (83%)	6/13 (46%)

* P = .038.
(Freeman DE, Mancuso AA, Parsons JT, Mendenhall WM, Million RR. Irradiation alone for supraglottic larynx carcinoma: can CT findings predict treatment results? Int J Radiat Oncol Biol Phys 1990;19:488)

TABLE 18-8. Supraglottic Carcinoma: Local Control With Radiotherapy as Related to Suitability for Supraglottic Laryngectomy: 103 Patients With 105 Evaluable Lesions (No. Controlled/No. Treated)*

Stage	Anatomically Suitable for Supraglottic Laryngectomy			Anatomically Not Suitable for Supraglottic Laryngectomy
	Medically Suitable	Medically Unsuitable	Total	
T1	7/7	5/5	12/12	1/1
T2	14/17 (82%)	8/9	22/26 (85%)	12/16 (75%)
T3	3/5	3/7	6/12 (50%)	19/29 (66%)
T4	1/3	0/1	1/4	2/5

* Excludes 26 patients who died within 2 years of radiotherapy with primary site continuously disease-free. (Mendenhall WM, Parsons JT, Stringer SP, Cassisi NJ, Million RR. Carcinoma of the supraglottic larynx: a basis for comparing the results of radiotherapy and surgery. Head Neck 1990;12:206)

Reduced mobility and fixation of the vocal cord are contraindications to supraglottic laryngectomy. These patients may be treated with radiation therapy, although the local control rates are poorer compared with those for patients with normal cord mobility (Table 18-9).

The status of the neck often determines the selection of treatment of the primary lesion. Patients with clinically negative neck nodes and a high risk for subclinical bilateral neck disease may be treated by radiation therapy because of the ease of bilateral elective neck irradiation. Alternatively, supraglottic laryngectomy and bilateral modified neck dissections may be done.[8]

When a patient has an early-stage primary lesion but advanced neck disease (N2B or N3), combined treatment is frequently necessary to produce a high rate of control of the neck disease. In these cases the primary lesion is usually treated for cure by irradiation, with neck dissection added to the involved side or sides of the neck (Fig. 18-28). If the patient has early, resectable neck disease and surgery is elected for the primary site, postoperative irradiation is only added for specific indications. We prefer to avoid routine high-dose preoperative or postoperative irradiation in conjunction with a supraglottic laryngectomy because the lymphedema of the remaining larynx may be considerable, although it will usually eventually subside.

ADVANCED SUPRAGLOTTIC LESIONS. The surgical treatment for these lesions is total laryngectomy. If neck disease is present and is resectable, then operation is the initial treatment, and postoperative irradiation is added if indicated. If the neck disease is unresectable, preoperative irradiation is used (see Chap. 6). A few selected advanced lesions, especially those that are mainly exophytic, may be considered for irradiation, and total laryngectomy is reserved for failure (Fig. 18-29). A dose of 5000 cGy is delivered, and if the response is good, irradiation is continued for cure (Fig. 18-30). If the response is unsatisfactory, irradiation is stopped and total laryngectomy is done 4 to 6 weeks later. There is no proof that one may select patients by this therapeutic trial, but many of the T3 and T4 successes are culled in this fashion.

Recent trials have used the response to chemotherapy to cull the advanced lesions suitable for attempted cure with irradiation.[12a,35,66,88a]

Surgical Treatment

SUPRAGLOTTIC LARYNGECTOMY. Supraglottic laryngectomy is a voice-sparing operation that can be used successfully for selected lesions involving the epiglottis, a single arytenoid, the aryepiglottic fold, and the false vocal cord. Extension of the tumor to the true vocal cord, the anterior commissure, or both arytenoids, fixation of the vocal cord, or thyroid or cricoid cartilage invasion precludes supraglottic laryngectomy. The supraglottic laryngectomy may be extended to include the base of the tongue as long as one lingual artery is preserved. To extend the procedure for involvement of the base of the tongue, the tongue extension must be lateralized to one side and should not extend beyond the cir-

(*text continues on page 474*)

TABLE 18-9. Supraglottic Carcinoma: Local Control With Radiotherapy Related to Cord Mobility in 83 Patients With 83 Evaluable Lesions (No. Controlled/No. Treated)

Stage	Cord Mobility			
	Mobile	Decreased	Fixed	Not Stated
T2	29/33 (88%)	2/5	No data	3/4
T3	18/28 (64%)	3/6	3/6	1/1

(Mendenhall WM, Parsons JT, Stringer SP, Cassisi NJ, Million RR. Carcinoma of the supraglottic larynx: a basis for comparing the results of radiotherapy and surgery. Head Neck 1990;12:207)

Figure 18-28. A 68-year-old man who was admitted for a lens implant was noted to have a mass in the left upper neck. Examination revealed a squamous cell carcinoma of the infrahyoid epiglottis with multiple bilateral neck nodes (T2N3B). The largest lymph node on the left was 5×3 cm and the largest lymph node on the right was 3×2 cm. All of the lymph nodes were mobile. (For color photographs, see Color Fig. *C* and *D* in Chap. 3.) (*A*) Lesion of the infrahyoid epiglottis with minimal extension to the aryepiglottic fold and pharyngoepiglottic fold. It was elected to treat the primary lesion with radiation therapy because of the desirability of combining radiation therapy and neck dissection for management of the neck. High-energy x-rays (17 MV) were selected in view of the planned bilateral neck dissection. The radiation treatment plan included 7000 cGy over 7 weeks, 17-MV x-rays, to the primary lesion and upper neck. The lower neck received 5000 cGy over 5 weeks, 8-MV x-rays. The posterior upper neck received 1000 cGy, 10-MeV electrons. Staged neck dissection followed at 1 month and 2 months after radiation therapy. (*B*) Appearance of right side of neck after radical neck dissection; no tumor was found in 16 lymph nodes. (*C*) Appearance of left side of neck after radical neck dissection; no tumor was found in 44 lymph nodes. There were no postoperative wound complications. Moderate facial and submental lymphedema slowly subsided over the next 3 months. (*D*) At 20 months there was essentially no edema. The patient died without tumor recurrence 7 years after treatment.

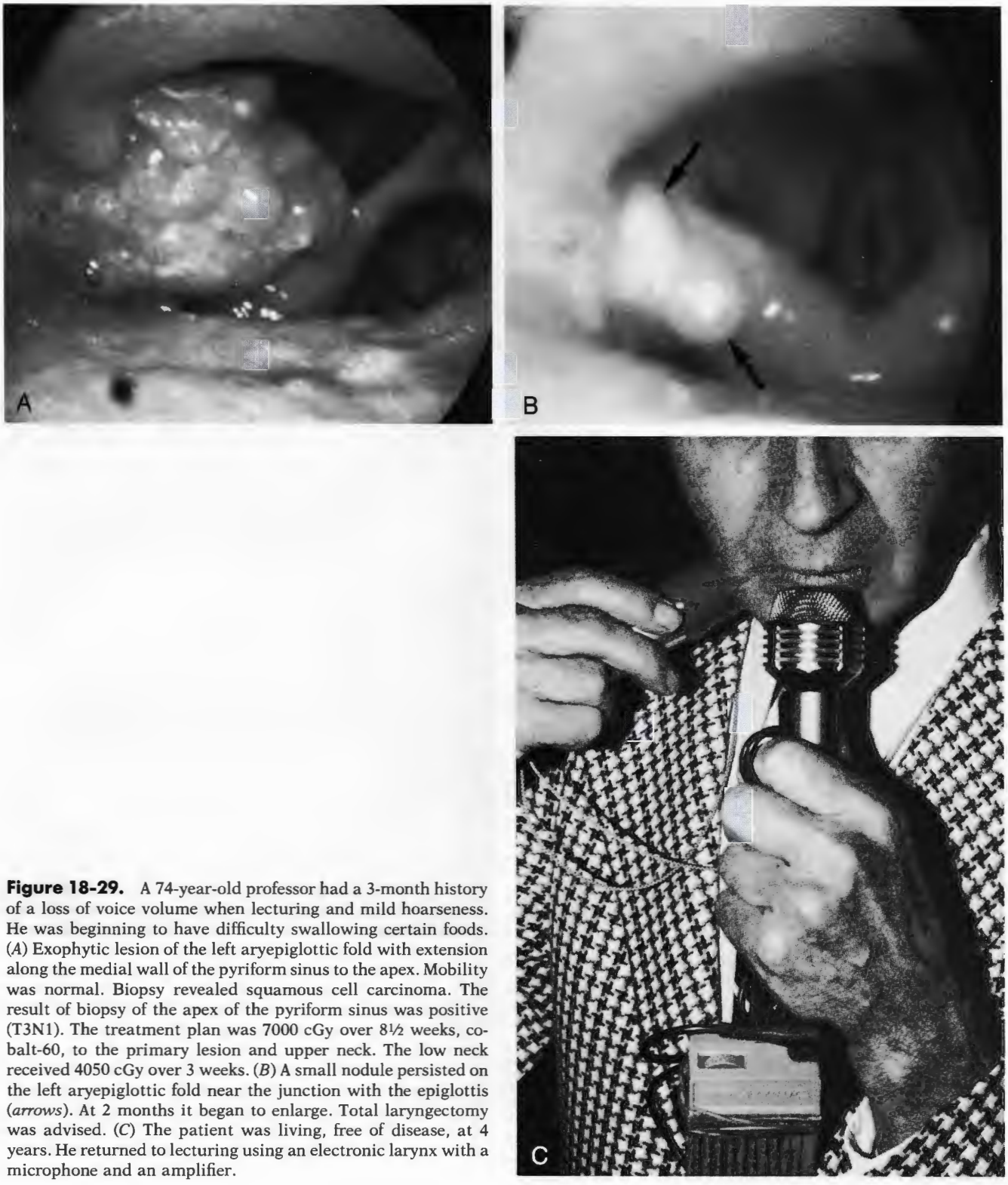

Figure 18-29. A 74-year-old professor had a 3-month history of a loss of voice volume when lecturing and mild hoarseness. He was beginning to have difficulty swallowing certain foods. (*A*) Exophytic lesion of the left aryepiglottic fold with extension along the medial wall of the pyriform sinus to the apex. Mobility was normal. Biopsy revealed squamous cell carcinoma. The result of biopsy of the apex of the pyriform sinus was positive (T3N1). The treatment plan was 7000 cGy over 8½ weeks, cobalt-60, to the primary lesion and upper neck. The low neck received 4050 cGy over 3 weeks. (*B*) A small nodule persisted on the left aryepiglottic fold near the junction with the epiglottis (*arrows*). At 2 months it began to enlarge. Total laryngectomy was advised. (*C*) The patient was living, free of disease, at 4 years. He returned to lecturing using an electronic larynx with a microphone and an amplifier.

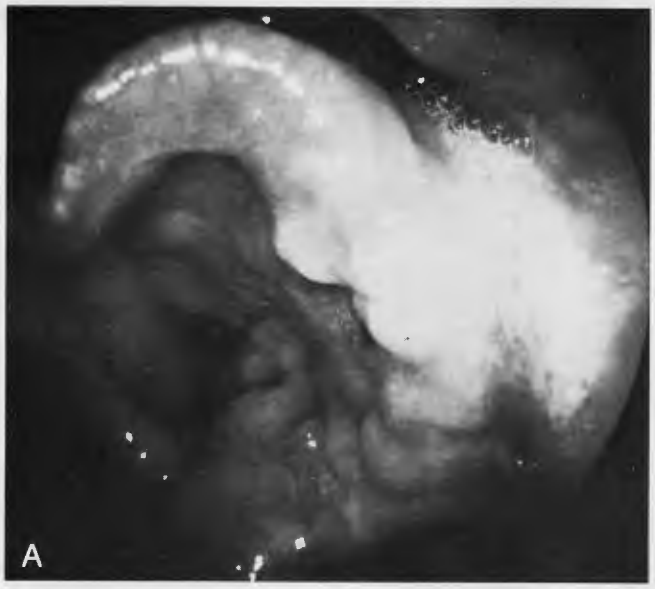

Figure 18-30. (*A*) Squamous cell carcinoma of the right aryepiglottic fold with extension to the false cord, pharyngoepiglottic fold, and vallecula and across the midline of the epiglottis (T3N0) in a 52-year-old woman. The surgical alternative was total laryngectomy. The treatment plan was 5000 cGy and reevaluation. (*B*) External-beam portal (4600 cGy over 4 weeks, cobalt-60, given as 120 cGy twice a day). The lower border was located at the bottom of the cricoid cartilage. A small strip of skin was spared in the submental area. (*C*) There was an estimated 65% regression at 4500 cGy, and it was recommended that full-dose radiation therapy be completed. (*D*) Reduced external-beam right lateral portal. The final dose was 7680 cGy tumor dose (120 cGy twice a day). (*E*) The patient was free of disease at 10 years. (For color photograph see Color Fig. 6*A* through *C* in Chap. 3.) Note minor persistent anatomic distortion of the left arytenoid and false cord.

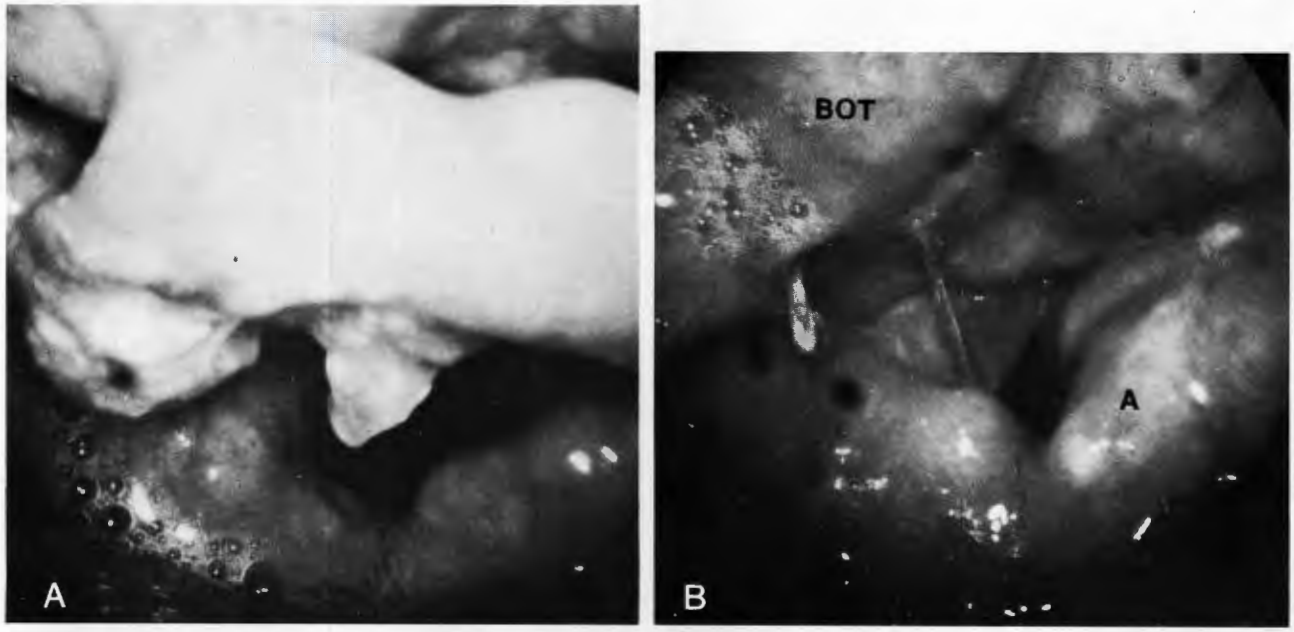

Figure 18-31. (*A*) Squamous cell carcinoma of the infrahyoid epiglottis (T2N0). A trial of radiation therapy was recommended, but there was minimal regression after 4000 cGy over 4 weeks. Radiation therapy was discontinued and supraglottic laryngectomy was performed 1 month later. (*B*) Appearance 3 months following supraglottic laryngectomy. There was 2+ lymphedema, but the voice was normal and the patient swallowed without aspiration. He was free of disease at 3 years. BOT, base of the tongue; A, right arytenoid.

cumvallate papillae. A neck dissection for a clinically negative or positive neck is added as outlined in Chapter 6. For midline lesions with a clinically negative neck, functional neck dissection is done bilaterally.

All patients have difficulty swallowing with a tendency to aspirate in the immediate postoperative period, but almost all learn to swallow again in a short time; motivation and the amount of tissue removed are key factors in learning to swallow again. It is essential that adequate pulmonary reserve be present preoperatively, as evaluated by blood gas determinations, pulmonary function tests, chest roentgenography, and a work test (walking the patient up two flights of stairs to determine tolerance to pulmonary stress). The voice quality is generally normal after supraglottic laryngectomy.

Some centers use preoperative or postoperative irradiation as an adjunct to supraglottic laryngectomy. Routine use of preoperative irradiation is not indicated in carefully selected cases, since the cure rate with surgery alone is quite high and radiation therapy increases the surgical complications and promotes lymphedema without substantially affecting the cure rate (Fig. 18-31). Postoperative radiation therapy may be advised for close or positive margins or when the risk of neck failure is substantial.[68]

The structures removed include the entire epiglottis, both false vocal cords, the aryepiglottic folds, the preepiglottic space, a portion or all of the hyoid bone and thyroid cartilage, and, in some instances, one arytenoid. The neck incision is usually a modified Schobinger or an apron flap. The neck dissection is completed and left attached to the thyrohyoid membrane. The supraglottic laryngectomy is outlined in Figure 18-32. The perichondrium of the larynx is elevated in continuity with the strap muscles and preserved to help close the surgical defect. Saw cuts are made through the thyroid cartilage and the hyoid bone so that the preepiglottic space is included in the specimen. Only the arytenoids and true

Figure 18-32. Supraglottic laryngectomy. Inset shows modified Schobinger skin incision. (*A*) Saw ► cuts on thyroid cartilage after the muscles and perichondrium have been reflected. The hyoid bone has been skeletonized. (*B*) Scissors cut through suprahyoid muscles to gain entrance into the pharynx by way of the vallecula for exposure of lesions of the false cord, pyriform sinus, or laryngeal surface of epiglottis. (*C*) Scissors cut through the pharyngeal constrictors to gain entrance into the pharynx by way of the pyriform sinus for lesions of the vallecula or lingual surface of the epiglottis. At this point the lesion can be seen, and the remainder of the incision (shown in D) is made under direct vision. (*D*) The incision into the pyriform sinus (in C) is extended superiorly through the suprahyoid muscles and the base of the tongue. (*E*) Removal of supraglottic lesion; both arytenoids are preserved. (*F*) Removal of supraglottic lesion including one arytenoid. (*G*) Closure of the defect, suturing muscle and perichondrium (inferiorly) to base of the tongue (superiorly). (*H*) Larynx after supraglottic laryngectomy (no irradiation). The base of the tongue extends to the anterior commissure of the glottis.

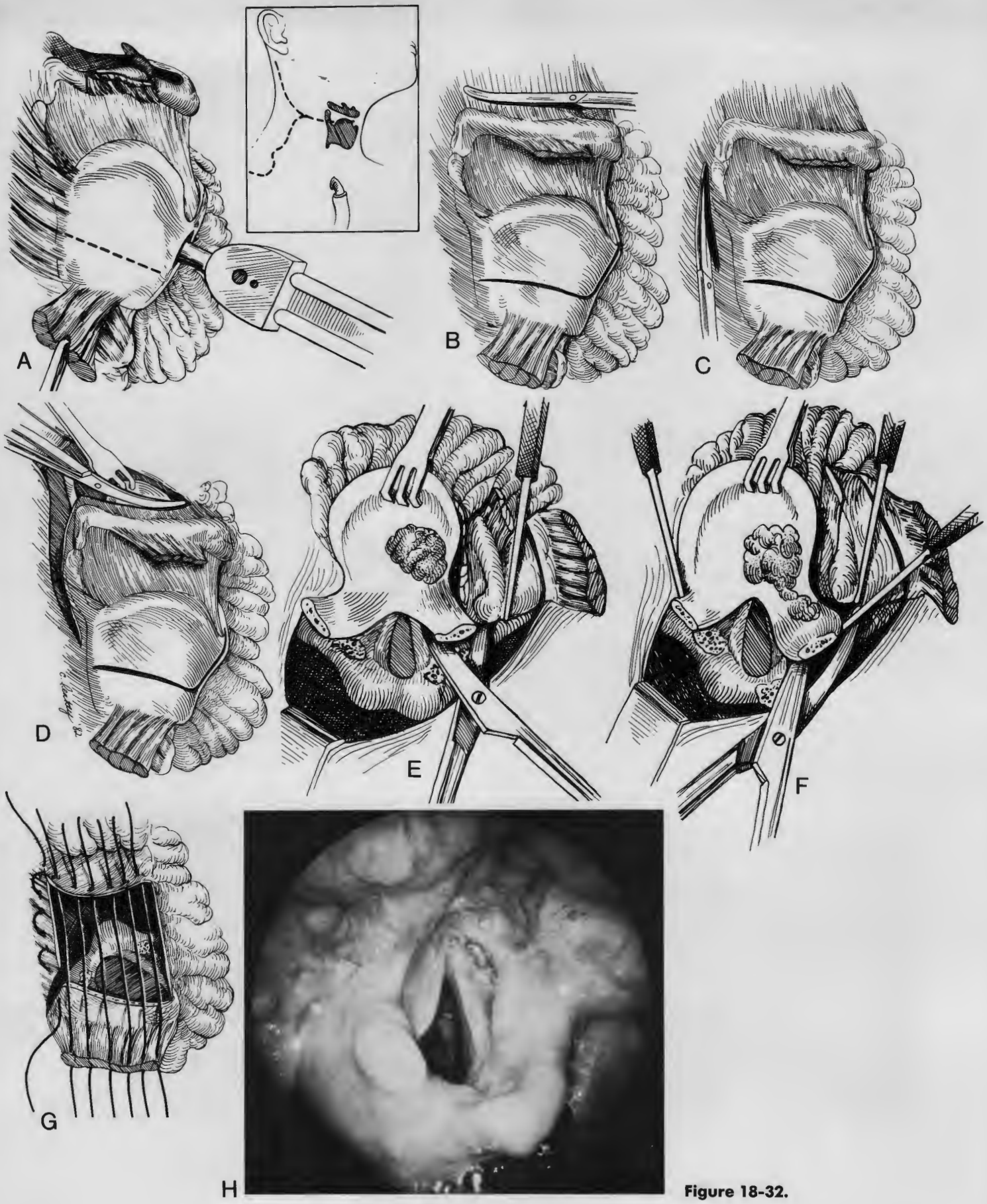

Figure 18-32.

vocal cords remain after the specimen is removed. If one arytenoid must be sacrificed, the ipsilateral cord must be fixed in the midline to prevent aspiration. The defect is closed by suturing the previously saved perichondrium and muscle to the base of the tongue. Ten to 14 days later, the tracheostomy and nasogastric tubes are removed and the patient is retrained in the act of swallowing. The patient is discharged when 2000 mL or more can be swallowed without significant aspiration. A temporary gastrostomy may be required when the base of the tongue is resected, and it may remain as long as 3 months. Less than 5% of cases are converted to total laryngectomy at the time of operation with careful preoperative assessment.

WIDE-FIELD TOTAL LARYNGECTOMY. The entire larynx and preepiglottic space are resected en bloc and a permanent tracheostomy is fashioned. The strap muscles, the hyoid bone, and a portion of the thyroid gland are included with the specimen. The pharynx is reconstituted in most cases without a flap. Neck dissection is added as outlined in Chapter 6. The lateral paratracheal lymph nodes are included and removed to the level of the stoma.

Irradiation Technique

The primary lesion and both sides of the neck are included with opposed lateral portals; wedges are used to compensate for the contour of the neck (Fig. 18-33). The anterior midline skin is shielded for lesions limited to the suprahyoid epiglottis, arytenoids, and aryepiglottic folds. It is usually not possible to shield the anterior midline skin for lesions of the infrahyoid epiglottis, false vocal cords, or whenever there is significant tumor involvement of the preepiglottic space. (See also the section on irradiation technique in Chap. 20.)

The inferior margin of the portal is usually 2 to 3 cm below the gross disease.

For the clinically negative neck, the posterior border is just behind the sternocleidomastoid muscle and the superior border encompasses the subdigastric lymph nodes to a level just below the tip of the mastoid. The neck margins are increased to include the posterior cervical chain and the junctional lymph nodes when the nodes are clinically positive.

The lower neck nodes are irradiated through a separate anterior portal; the midline shield in the low neck portal should be narrow to treat the lateral paratracheal lymph nodes, which lie in the tracheoesophageal groove (Fig. 18-34).

The beam energy is ^{60}Co or 4 MV. There is a potential for underdosing anterior structures with 6 MV.

The dose for T1 lesions is 6000 cGy over 6 weeks to 6400 cGy over 7 weeks and for T2 and T3 lesions, 6400 cGy to 7000 cGy. (See also Chap. 12.) The early lesions that are encompassed by a small treatment volume receive 200 cGy per fraction. The lesions requiring a large treatment volume receive 180 cGy per fraction for the first 4500 to 5040 cGy and 200 cGy per fraction for the reduced portal. Hyperfractionation, 120 cGy twice a day, has been used since 1978 for T2 to T4 lesions. The total dose is 7440 to 7680 cGy; higher doses to the larynx are not well tolerated.

An anterior submental "boost" portal with photons or electrons may be used for the last 500 to 1000 cGy for suprahyoid epiglottis lesions that invade the vallecula. (See Fig. 17-17 and the section on irradiation technique for the base of the tongue in Chap. 17.)

The addition of a neck dissection usually increases the risk of temporary lymphedema; however, neck dissection produces a higher control rate for neck disease and is preferable to the higher doses of radiation therapy required to control large neck nodes. (See Chap. 6.)

Patients develop a sore throat, loss of taste, and moderate dryness during irradiation. Edema of the arytenoids may occur and give a sensation of lump in the throat. Tracheostomy is seldom necessary even for bulky lesions.

Figure 18-33. Treatment portals for the primary site in carcinoma of the supraglottic larynx. (*A*) Patient in treatment position using a face mask of nonfilled low-temperature thermal plastic (polycaprolactone) to immobilize the head. (*B*) Clothespins are used to increase the amount of tissue spared anteriorly. (Mendenhall WM, Million RR, Cassisi NJ. Squamous cell carcinoma of the supraglottic larynx treated with radical irradiation: analysis of treatment parameters and results. Int J Radiat Oncol Biol Phys 1984;10:2226)

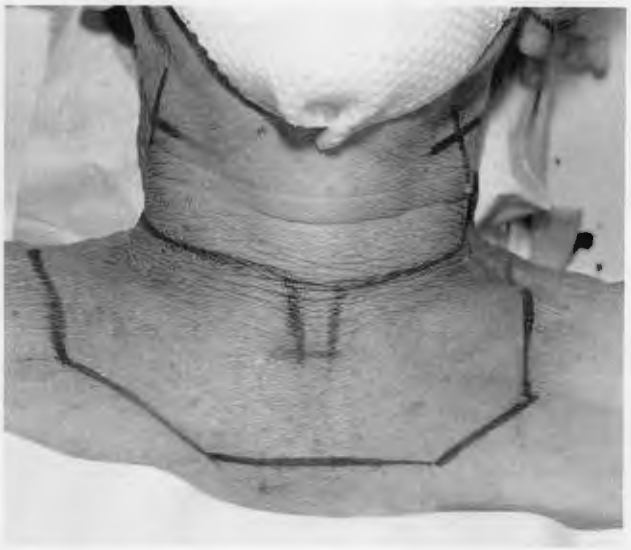

Figure 18-34. Carcinoma of the supraglottic larynx: Low neck treatment portal with midline block. (Mendenhall WM, Million RR, Cassisi NJ. Squamous cell carcinoma of the supraglottic larynx treated with radical irradiation: analysis of treatment parameters and results. Int J Radiat Oncol Biol Phys 1984;10:2229)

Edema of the larynx may persist for several months to a year. Minor anatomic distortions may persist after successful irradiation, especially in the more advanced cases (see Fig. 18-30). Neck dissection increases the degree of lymphedema on the side of the operation. The lymphedema of the larynx and submental space resolves together. Patients who continue to smoke heighten the side effects of dryness, dysphagia, and hoarseness.

Combined Treatment Policies

Laryngectomy has a high rate of success by itself for T3 lesions, and irradiation should only be added when indications are present. T4 lesions generally receive postoperative irradiation. Radiation therapy is added for close or positive margins, invasion of soft tissues of the neck, subglottic extension, cartilage invasion, multiple positive lymph nodes, and extracapsular extension. Preepiglottic space invasion per se is not an indication for irradiation. If total laryngectomy is required and the lesion is resectable, postoperative irradiation is preferred, since there is no evidence that preoperative irradiation produces any better local-regional control or survival rates. The high-risk areas for recurrence are usually the base of the tongue and the neck; the stomal area is mainly at risk when subglottic extension is present, but it usually may be shielded. Complications related to postoperative irradiation are relatively uncommon in this group if the pharyngeal wall is not resected.

Irradiation is used before total laryngectomy for patients with technically unresectable neck nodes and as a trial of radiation therapy before deciding on radiation therapy alone or total laryngectomy.

A number of patients either refuse laryngectomy or are unsuitable medically for the operation, and irradiation is the treatment by default. A few of these patients can be cured, however, and one should not take a hopeless attitude.[18]

Management of Recurrence

Failures after supraglottic laryngectomy or irradiation can frequently be salvaged by further treatment, and recognition of recurrence should be vigorously pursued. Supraglottic laryngectomy can be used for selected irradiation failures. Salvage of recurrence after combined total laryngectomy and radiation therapy is uncommon. Stomal recurrences are sometimes controlled by radiation therapy or surgery.

RESULTS OF TREATMENT

Vocal Cord Cancer

Surgical Results

Wetmore and associates treated 21 vocal cord lesions with CO_2 laser excision (T1, 16 patients; carcinoma in situ, 5 patients). Four developed local recurrence and were salvaged by radiation therapy (3 patients) or repeat laser (1 patient). Three of the recurrences occurred at the anterior commissure. Voice quality was reported as generally serviceable but having a harsh quality—better than after cordectomy or hemilaryngectomy and not as good as after radiation therapy. Vocal quality varied with the amount of vocalis muscle and mucosa resected.[87]

Neel and coworkers reported the results for 182 patients with early vocal cord carcinoma suitable for cordectomy; 177 had lesions that were confined to one cord.[55] The lesions ranged from 2 to 25 mm in length. The follow-up was less than 3 years in 18% of cases. Four patients developed a laryngeal recurrence and 3 developed a neck recurrence. Only 3 patients (2%) died of their vocal cord cancer.

Ogura and associates reported a 3-year disease-free survival rate of 91% for 281 patients treated by hemilaryngectomy.[58] The local recurrence rate was 4% and the neck recurrence rate was 2%; 74% of treatment failures were salvaged.

A review of 61 patients with involvement of the anterior commissure treated by hemilaryngectomy resulted in an absolute survival of 74%.[72] There were three local recurrences (5%) and three neck recurrences (5%).

Som reported the results for hemilaryngectomy including the ipsilateral arytenoid for 130 cases of vocal cord carcinoma extending posteriorly to the vocal process and face of the arytenoid.[77] The cure rate for 104 patients with a T2 lesion was 74%, and for 26 patients with a T3 lesion it was 58%.

Bauer and coworkers analyzed the significance of the surgical margins in 111 hemilaryngectomy specimens.[5] Thirty-nine patients (35%) were found to have involved margins (usually the anterior margin). The local recurrence rate was 10% with a 5-year minimum follow-up. Seven recurrences were anterior. Only seven (18%) of the 39 patients with an involved margin developed a recurrence, compared with 6% with uninvolved margins. Additionally, 5% had recurrence evident in the cervical lymph nodes. Four patients eventually died of cancer.

Ogura and coworkers reported that the 3-year cause-specific disease-free survival rate for patients treated by total laryngectomy with or without radical neck dissection was 80%.[58] The local and regional recurrence rate

TABLE 18-10. Literature Results of Stage T4 Glottic Cancer

Author	Stage	No. Patients	Method of Treatment	Results (NED)
Jesse[36]	T4 N0–N+	48	Laryngectomy	54% at 4 years
Ogura and coworkers[58]	T4 N0	11	Laryngectomy	45% at 3 years
Skolnick and coworkers[75]	T4 N0	7	Laryngectomy	30% at 5 years
Vermund[81]	T4 N0	31	Laryngectomy	35% at 5 years
Stewart and Jackson[79]	T4 N0	13	Irradiation with surgery for salvage	38% at 5 years
Harwood and coworkers[33]	T4 N0	56	Irradiation with surgery for salvage	49% at 5 years*

NED, no evidence of disease.

* Actuarial survival, uncorrected for deaths due to intercurrent disease.

(Modified with permission from Harwood AR, Beale FA, Cummings BJ, Keane TJ, Payne D, Rider WD. T4N0M0 glottic cancer: an analysis of dose-time volume factors. Int J Radiat Oncol Biol Phys 1981;7:1507–1511. Copyright © 1981, Pergamon Press, Ltd)

was 21%; about 46% of treatment failures were salvaged by surgery or radiation therapy, alone or combined.

The results of treatment of T4 vocal cord carcinoma from four surgical series and two irradiation series are summarized in Table 18-10.[32,33,36,58,75,79,81]

Mendenhall and associates reviewed 118 previously untreated patients with T3 carcinoma treated by irradiation and/or laryngectomy between 1965 and 1988. The results are given in Table 18-11.[50] The patients selected for irradiation alone generally had smaller-volume primary lesions. The total risk of a complication (including salvage procedures) was similar.

Yuen and coworkers from the M. D. Anderson Hospital reviewed 185 patients with T3 glottic cancer treated with surgery alone (155 patients) or combined with postoperative irradiation (30 patients). All patients underwent a total laryngectomy. Local-regional recurrence occurred in 17%. The 5-year disease-free survival rate was 80% after surgery alone and 90% after surgery and postoperative irradiation.[90]

A Mayo Clinic series included 106 patients with T3 glottic carcinoma treated with curative intent by surgery (104 patients) or irradiation alone (2 patients). Included in the surgically treated group were 12 patients in whom prior radiation therapy had failed. Six percent of the patients had recurrence at the primary site and 15% had recurrence in the neck nodes. An 80% cause-specific survival was reported with a 2½-year minimum follow-up.[13]

Radiation Therapy Results

The appearance of a variety of lesions before and after radiation therapy is shown in Figures 18-35 through 18-38.

Harwood selectively treated 11 patients with hyperkeratosis; all were free of disease after 1 to 15 years.[30] Pêne and Fletcher reported the results for 79 patients with carcinoma in situ and 7 with dysplasia.[65] The local failure rate was 11% for lesions with a T1 anatomic distribution and 26% for lesions with a T2 anatomic distribution. Elman and coworkers reported similar results.[15]

The modern-day local control rates reported from several institutions for invasive squamous cell carcinoma are in the range of 90% for T1, 70% to 80% for T2, and 50% to 71% for T3 disease. The surgical salvage rate for T1 and T2 irradiation failures is about 70%, and for T3 lesions it is 50% to 70%.

Mendenhall and coworkers reported the radiation therapy results for 304 patients with T1–T2 squamous cell carcinomas of the vocal cord treatment between 1964 and 1984.[47] During the 20-year period essentially all T1—T2 patients were treated initially by radiation therapy. Patients were further stratified by anatomic extent and as to the most conservative operation required to remove the lesion.[48] The rates of local control and surgical salvage for each subgroup are shown in Table 18-12.

(text continues on page 481)

TABLE 18-11. T3 Vocal Cord Carcinoma: A Comparison of Radiation Therapy and Surgery at the University of Florida, 1965–1988, 118 Patients: 5-Year Results*†

Treatment Modality	No. Patients	No. Excluded	Local-Regional Control	Salvage	Ultimate Local-Regional Control	Complications			Laryngeal Voice Preservation	5-Year Survival	
						Initial Therapy	Salvage	Total		Absolute	Cause-Specific
Radiation therapy	53	6	62%	9/15	84%	3/53	5/15	16%	63%	55%	75%
Surgery ± radiation therapy	65	13	75%	2/7	82%	10/65	0/7	15%	6%	45%	71%

* Calculated by the Kaplan-Meier product-limit method.[37,69]

† 98% of recurrences were noted within 5 years.

(Data from Mendenhall WM, Parsons JT, Stringer SP, Cassisi NJ, Million RR. Stage T3 squamous cell carcinoma of the glottic larynx: a comparison of laryngectomy and irradiation. Int J Radiat Oncol Biol Phys 1992;23:725–732)

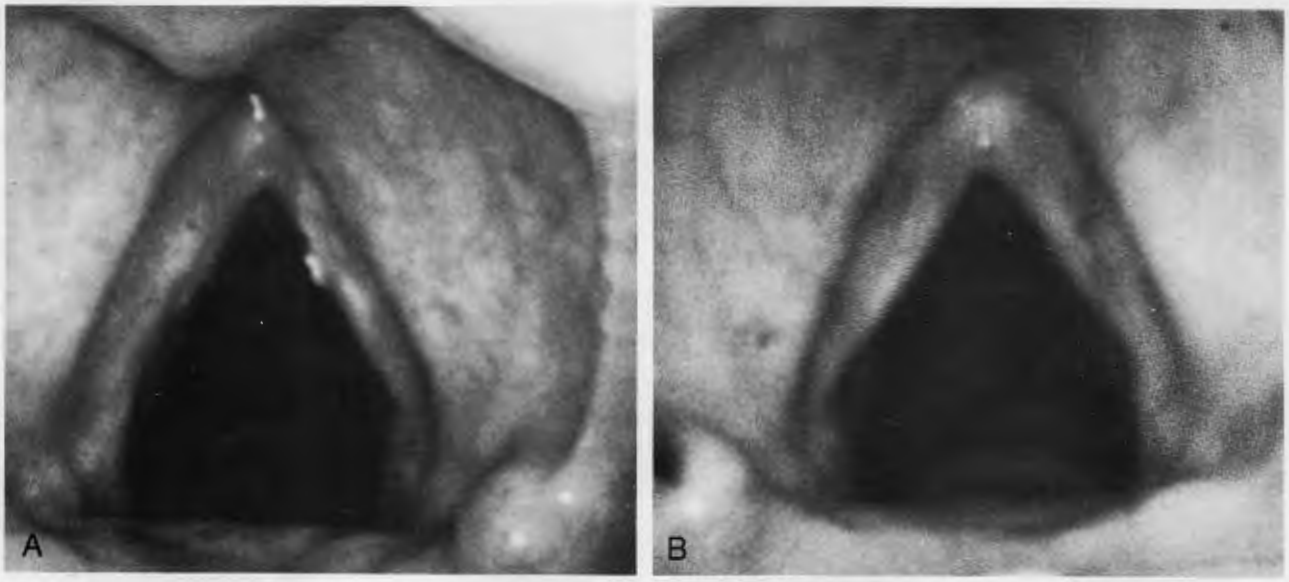

Figure 18-35. (*A*) Invasive squamous cell carcinoma (2 mm) of the right vocal cord (T1N0). Treatment was 5625 cGy over 5 weeks, cobalt-60. (*B*) Appearance of larynx 17 months after treatment. The patient was free of disease at 5 years.

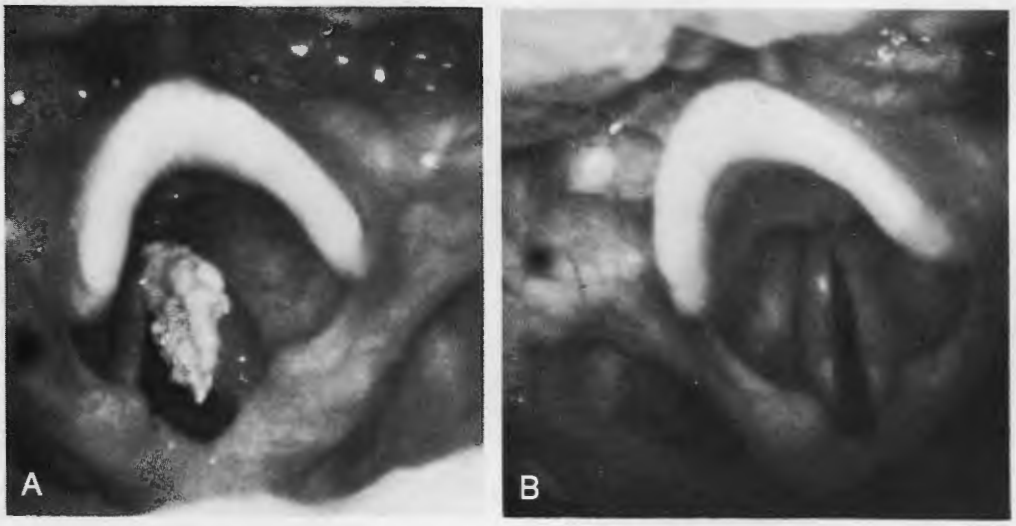

Figure 18-36. A 43-year-old man had a history of hoarseness for 1½ years before admission. Excisional biopsy of a right vocal cord lesion 1 year before admission revealed no cancer. He developed recurrent hoarseness, and rebiopsy 4 months before admission revealed verrucous carcinoma. Hoarseness did not improve, and lesion was growing. (*A*) Warty lesion of right vocal cord with extension to anterior commissure; mobility was normal. The right posterior cord was edematous and erythematous to the arytenoid. Rebiopsy revealed moderately well-differentiated squamous cell carcinoma (T1N0). Treatment was 6300 cGy in 28 fractions over 5½ weeks. (*B*) Appearance at 15 months. The patient was free of disease at 11 years.

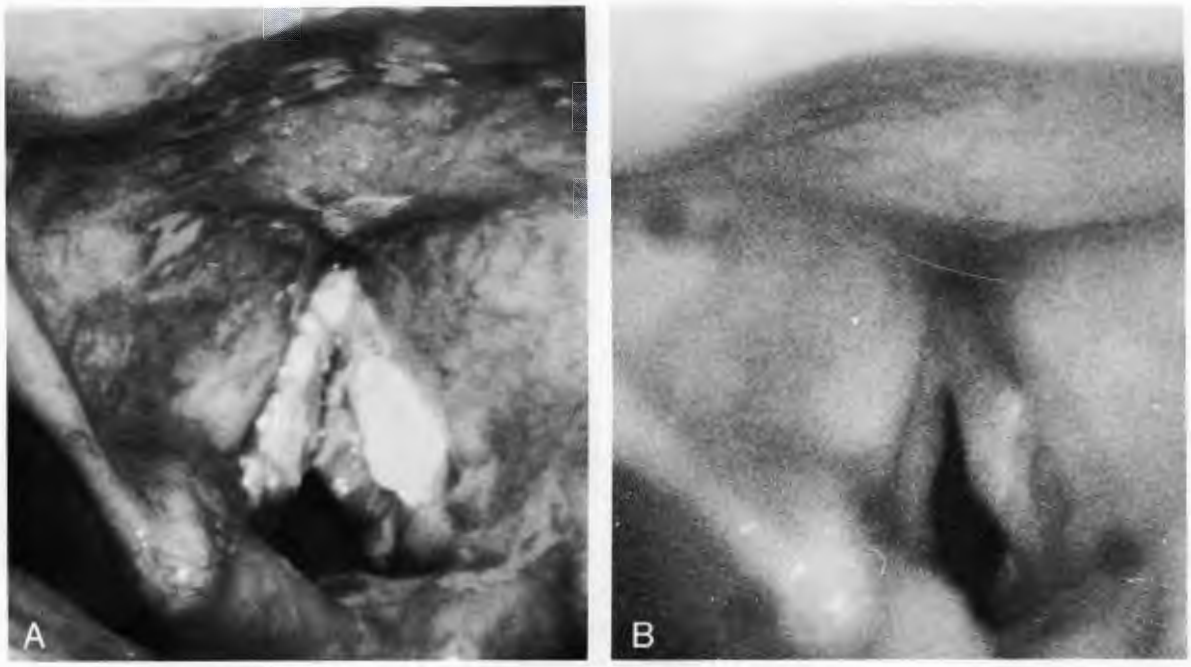

Figure 18-37. (*A*) Squamous cell carcinoma of both vocal cords with 1.0 to 1.5-cm subglottic extension and early involvement of the right false vocal cord. Both cords were mobile (T2N0). Treatment was 6300 cGy in 28 fractions over 5 weeks, ^{60}Co. (*B*) There was no evidence of disease at 7 years. (For color photograph see Color Fig. 2*A* and *B* in Chap. 3.)

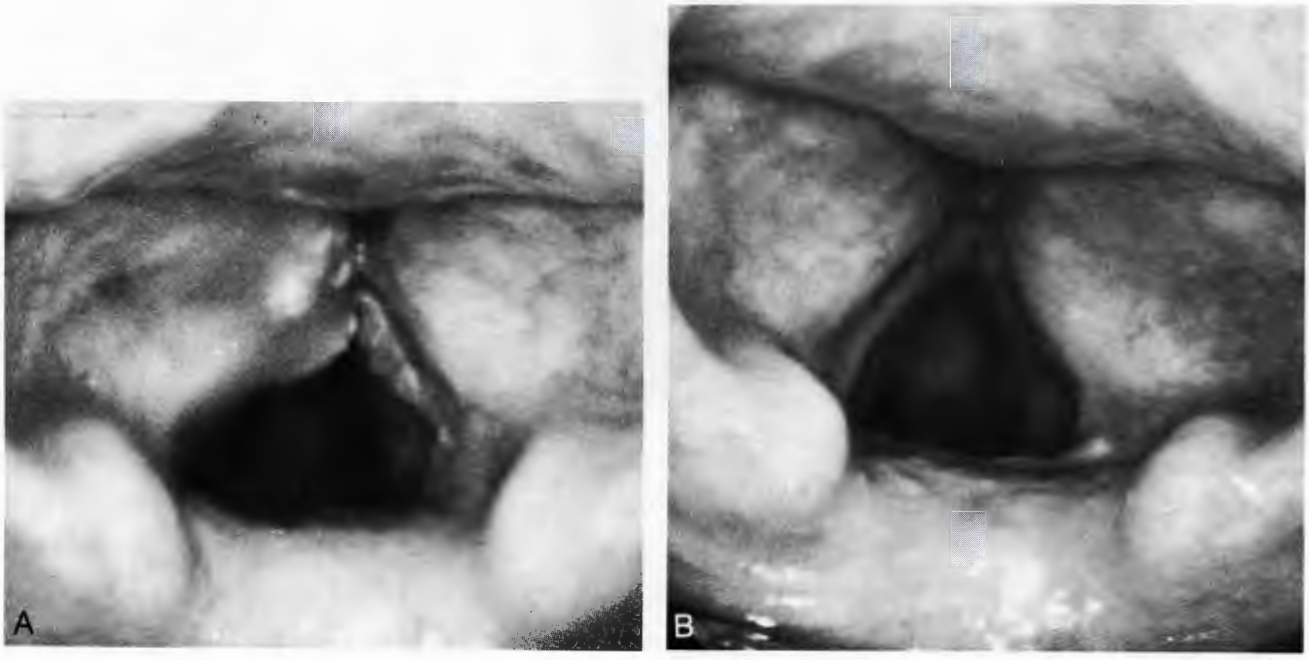

Figure 18-38. (*A*) Squamous cell carcinoma of both vocal cords with involvement of the anterior commissure, left anterior false cord, and petiole of the epiglottis. There was reduced mobility of left vocal cord (T2N0). Treatment was 6750 cGy in 30 fractions over 6 weeks, ^{60}Co. (*B*) Appearance at 1 month after completion of therapy. The patient was free of disease at 4½ years. (For color photographs see Color Fig. 2 *C* and *D* in Chap. 3.)

TABLE 18-12. T1–T2 Vocal Cord Carcinoma Treated by Irradiation: Local Control Analyzed by Anatomic Extent and the Surgical Procedure Required—304 Patients (No. Controlled/No. Treated)

T Stage	Surgical Subgroup*	Size	Excluded†	Local Control (%)	No. Salvaged‡/No. Attempted		Ultimate Local Control (%)
					Hemilaryngectomy	Total Laryngectomy	
T1a	C	<5 mm	1	12/12 (100)	No data	No data	12/12 (100)
		5–15 mm	8	73/78 (94)	3/4	0/1	76/78 (97)
		>15 mm	2	45/50 (90)	No data	4/5	49/50 (98)
T1b	HL	All	0	14/15 (93)	No data	0/1	14/15 (93)
	TL	All	2	15/16 (94)	0/1	No data	15/16 (94)
T2a	HL	All	5	23/27 (85)	No data	4/4	27/27 (100)
	TL	All	2	27/38 (71)	2/3	7/8	36/38 (95)
T2b	HL	All	3	13/18 (72)	1/2	2/3	16/18 (89)
	TL	All	2	18/25 (72)	No data	4/6	22/25 (88)

* C, suitable for cordectomy; HL, suitable for hemilaryngectomy; TL, suitable for total laryngectomy.
† Died less than 2 years after treatment and continuously free of disease.
‡ Salvage after a local recurrence was defined as no evidence of recurrent disease at the primary site for at least 1 year after surgery with unlimited follow-up.
(Mendenhall WM, Parsons JT, Stringer SP, Cassisi NJ, Million RR. T1–T2 vocal cord carcinoma: a basis for comparing the results of radiotherapy and surgery. Head Neck Surg 1988;10:375)

Overall voice preservation (including patients dying of intercurrent disease prior to 2 years of evaluation and patients salvaged by hemilaryngectomy) is shown in Table 18-13. Hemilaryngectomy was not used as a salvage procedure until 1973. Within each subgroup there was no difference in the rate of local recurrence based on whether the anterior commissure was involved. In 19 women (13 with T1 and 6 with T2 lesions), all lesions were controlled. Control of neck disease for T1 and T2 lesions is discussed in the section on lymphatic spread in this chapter. The 5-year absolute and cause-specific survival rates are given in Table 18-14; the 5-year rate of intercurrent death was 13%.

T2 lesions have been managed since 1986 by 120 cGy given twice daily for a dose of 7440 cGy. The local control rate for 28 patients with a minimum 2-year follow-up is 93% (Parsons JT, personal communication, February 1991).

TABLE 18-13. T1–T2 Vocal Cord Carcinoma: Voice Preservation—304 Patients (No. Patients With Voice Preservation/ No. Treated)

T Stage	Subgroup	Size	Proportion With Voice Preservation (%)
T1a	C	<5 mm	13/13 (100)
		5–15 mm	83/86 (97)
		>15 mm	47/52 (90)
T1b	HL	All	14/15 (93)
	TL	All	17/18 (94)
T2a	HL	All	28/32 (88)
	TL	All	31/40 (78)
T2b	HL	All	17/21 (81)
	TL	All	20/27 (74)

C, suitable for cordectomy; HL, suitable for hemilaryngectomy; TL, suitable for total laryngectamy.
(Mendenhall WM, Parsons JT, Stringer SP, Cassisi NJ, Million RR. T1–T2 vocal card carcinoma: a basis for comparing the results of radiotherapy and surgery. Head Neck Surg 1988;10:375)

T3 Results

The local and ultimate control rates for eight series of T3 lesions treated by radiation therapy are given in Table 18-15.[19,31,50,54,62,76,78,84]

Mendenhall and coworkers updated the results for 53 patients with T3 lesions treated by irradiation between 1965 and 1988. Four patients refused laryngectomy and 2 were medically inoperable; the remaining 47 patients were offered irradiation rather than laryngectomy. The percentage of T3 patients managed by irradiation increased through the study period: 1965 to 1969, 20%; 1970 to 1979, 30%; 1980 to 1988, 67%. Five-year results were given in Table 18-11.[50] Assessment of cord mobility at 5000 cGy, at the end of treatment, and at 1 month after treatment did not correlate with local control. The cord may remain fixed in patients who are cured. Cord fixation developing after return of mobility was associated

TABLE 18-14. T1–T2 Vocal Cord Carcinoma: Five-Year Survival* (304 Patients)

Stage	Subgroup	Absolute (%)	Cause-Specific (%)
T1aN0	C	107/122 (88)	107/110 (97)
T1bN0	HL	12/13 (92)	12/12 (100)
	TL	11/16 (69)	11/12 (92)
T2aN0	HL	16/23 (70)	16/18 (89)
	TL	27/34 (79)	27/28 (96)
T2bN0	HL	11/16 (69)	11/13 (85)
	TL	18/22 (82)	18/20 (90)

C, suitable for cordectomy; HL, suitable for hemilaryngectomy; TL, suitable for total laryngectomy.
* Excludes 3 patients with synchronous primary head and neck cancers and 1 patient with clinically positive neck nodes at presentation.
(Mendenhall WM, Parsons JT, Stringer SP, Cassisi NJ, Million RR. T1–T2 vocal cord carcinoma: a basis for comparing the results of radiotherapy and surgery. Head Neck Surg 1988;10:376)

TABLE 18-15. T3 Glottic Cancer Treated With Irradiation Alone

Reference	Institution	No. Patients	Minimum Follow-up (years)	Locol Control (%)	Control After Salvage Surgery (%)
Mendenhall and coworkers, 1991[50]	University of Florida	15*	2	53	73 (11/15)
Harwood and coworkers, 1980[31]	Princess Margaret	112	3	51	77
Wang, 1987[84]	Massachusetts General	70	4	36	57
Fletcher, 1969[19]	M. D. Anderson Hospital	17	2	77	No data
Skolyszewski and Reinfuss, 1981[76]	15 European Centers	91	3	50	No data
Stewart and coworkers, 1975[78]	Manchester	67	10	57	67
Mills, 1979[54]	Capetown, South Africa	18	2	44	78
Mendenhall and coworkers, 1991[50]	University of Florida	28†	2	71	89 (25/28)

* Continuous-course, once-a-day treatment.
† Twice-a-day treatment.
(Modified from Parsons JT, Mendenhall WM, Mancuso AA, Cassisi NJ, Stringer SP, Million RR. Twice-a-day radiotherapy for T3 squamous cell carcinoma of the glottic larynx. Head Neck 1989;11:127)

with local recurrence in all but one case. Total laryngectomy resulted in successful salvage in 9 of 15 local failures.

Twenty-three patients staged T3N0 treated with irradiation with the primary site continuously free of disease were evaluable for neck control analysis. Four received incomplete elective neck irradiation; 1 suffered neck node recurrence and was salvaged with further irradiation. Nineteen patients received elective neck irradiation; 1 (5%) had a recurrence in the neck at the posterior margin of the irradiation field at 63 months. The recurrence was unresectable, and the patient died of recurrent tumor in the neck alone. Control of neck disease was obtained in all of six patients with N1 disease and two patients with N2B disease.

Distant metastasis occurred in 6% of the patients who remained continuously free of disease and in 17% of those with local-regional recurrence.

Supraglottic Larynx Cancer

Surgical Results

The 3-year cause-specific survival rates for 176 patients with supraglottic carcinoma managed by supraglottic laryngectomy are shown in Table 18-16; 109 patients received preoperative radiation therapy.[59] Only 11 patients (6%) developed local recurrence; salvage by total laryngectomy or radiation therapy proved successful in 5 patients. Seventeen had treatment failures in the neck, and salvage was achieved in 9. For patients with advanced lesions treated with preoperative radiation therapy followed by total laryngectomy and radical neck dissection, the 3- and 5-year survival rates were 70% and 67%, respectively.

Ogura and coworkers reported 59 patients with supraglottic carcinoma with extension to one arytenoid, treated by supraglottic laryngectomy; 56 of the patients had preoperative radiation therapy.[57] Five patients developed a local recurrence, and 6 developed a neck recurrence. Salvage by total laryngectomy or radiation therapy was obtained in 4 of these patients.

Bocca reported 250 cases of supraglottic carcinoma (T1 and T2) managed by supraglottic laryngectomy and bilateral elective (or therapeutic) neck dissection.[7] The local recurrence rate was 11%, and the neck recurrence rate was 5%; in 9 patients salvage was achieved by further therapy. The 5-year survival rate was 80%.

Lee and associates reviewed the M. D. Anderson Hospital experience for 60 patients with intermediate stage supraglottic carcinomas managed by supraglottic laryngectomy and neck dissection; 83% received postoperative irradiation usually 5500 cGy over 6 weeks.[42] Patients selected for supraglottic laryngectomy were usually staged as T2 to T3 with bulky lesions; only 15% of cases seen from 1974 to 1987 were treated by this plan. There

TABLE 18-16. Supraglottic Larynx Carcinoma: 3-Year Cause-Specific Survival After Supraglottic Laryngectomy (176 Patients)

	N0		N1–N3	
Primary Stage	No. Surviving/ No. at Risk	Percentage	No. Surviving/ No. at Risk	Percentage
T1	64/78	82%	8/14	57%
T2	23/34	68%	8/12	67%
T3	7/10	70%	2/3	67%
T4	9/12	75%	8/13	62%

(Ogura JH, Sessions DG, Spector GJ. Conservative surgery for epidermoid carcinoma of the supraglottic larynx. Laryngoscope 1975;85:1812)

TABLE 18-17. Supraglottic Carcinoma: Local Control With Radiotherapy—103 Patients With 105 Evaluable Lesions (No. Controlled/No. Treated)*

Stage	Suprahyoid Epiglottis	Infrahyoid Epiglottis	Aryepiglottic Fold	False Vocal Cord	Arytenoid	Pharyngoepiglottic Fold
T1	2/2	3/3	1/1	5/5	1/1	1/1
T2	11/14	12/15	2/2	9/11	No data	No data
T3	0/1	14/20	7/9	3/10	1/1	No data
T4	3/6	0/3	No data	No data	No data	No data

* Excludes 26 patients who died within 2 years of radiotherapy with the primary site continuously diseose-free.
(Mendenhall WM, Parsons JT, Stringer SP, Cassisi NJ, Million RR. Carcinoma of the supraglottic larynx: a basis for comparing the results of radiotherapy and surgery. Head Neck 1990;12:206)

were no local failures and four neck recurrences. The 5-year cause-specific survival was 91%, and the 5-year absolute survival was 73%.

Radiation Therapy Results

Mendenhall and associates reported the results for 129 patients treated by continuous-course radiation therapy with or without planned neck dissection. Local control rates according to T stage and anatomic site of origin are shown in Table 18-17. Five of 10 patients with T3 false vocal cord primary lesions had impaired vocal cord mobility. Local control rates with initial treatment and after salvage treatment are shown in Table 18-18. Two fractionation schedules are compared in Table 18-19. Control above the clavicles is listed in Table 18-20, and the 5-year survival according to stage is shown in Table 18-21. The likelihood of voice preservation is shown in Table 18-22.[49] See also Tables 18-6 to 18-9 for further data relating to local control by irradiation.

Combined Therapy Results

Weems and associates analyzed 195 patients and compared those managed by either surgery alone or surgery combined with preoperative or postoperative radiation therapy with those treated with irradiation. Thirty of the surgery group had supraglottic laryngectomy; 3 received preoperative radiation therapy, and 9 received postoperative radiation therapy. The results are shown in Tables 18-23 through 18-28.[86]

For the supraglottic laryngectomy group, 2 of 13 developed a local failure after surgery alone and 1 was salvaged by total laryngectomy; there was one local failure in 12 patients managed with combined treatment, and salvage was not successful.

There is poor initial and ultimate local control for T3 and T4 lesions treated by initial radiation therapy. For selected patients with stage IVA (ie, T1 to T2 and N2 or N3A neck disease), radiation therapy followed by planned neck dissection produces local-regional control with voice preservation and 5-year survival rates similar to total laryngectomy results (see Tables 18-26 and 18-28).

The results of laryngectomy alone and laryngectomy plus postoperative radiation therapy for resectable stage IV cases of squamous cell carcinoma of the supraglottic larynx reported by M. D. Anderson Hospital are compared in Tables 18-29 and 18-30.[17,25]

Subglottic Carcinoma

Selection of Treatment

The only surgical alternative is total laryngectomy with postoperative irradiation added as indicated. The cure rate for irradiation with laryngectomy reserved for local failure is equivalent to laryngectomy for early stages. The reported local control for T4 lesions treated by radiation therapy ranges from 30% to 50%, and irradiation may be offered as an alternative to immediate laryngectomy. There is a substantial risk of second neoplasms and other intercurrent deaths.

(*text continues on page 487*)

TABLE 18-18. Local Control of Supraglottic Larynx Carcinoma With Radiotherapy: 129 Patients With 131 Lesions (No. Controlled/No. Treated)

Stage	Excluded*	Control with Initial Therapy	No. Salvaged/ No. Attempted†	Ultimate Control
T1	3	13/13	No data	13/13
T2	11	34/42 (81%)	3/7	37/42 (88%)
T3	7	25/41 (61%)	9/13	34/41 (83%)
T4	5	3/9	3/3	6/9

* Excludes 26 patients who died within 2 years of radiotherapy with primary site continuously disease-free.
† One patient coded as "salvage failure" who died within 1 year after salvage surgery with no evidence of disease at the primary site.
(Adapted from Mendenhall WM, Parsons JT, Stringer SP, Cassisi NJ, Million RR. Carcinoma of the supraglottic larynx: a basis for comparing the results of radiotherapy and surgery. Head Neck Surg 1990;12:205)

TABLE 18-19. Local Control of Supraglottic Larynx Carcinoma With Radiotherapy: 129 Patients With 131 Lesions (No. Controlled/No. Treated)

Stage	Once-a-day Fractionation	Twice-a-day Fractionation
T1	11/11	2/2
T2	23/29 (79%)	11/13 (85%)
T3	4/9	21/32 (66%)
T4	2/8	1/1

(Adapted from Mendenhall WM, Parsons JT, Stringer SP, Cassisi NJ, Million RR. Carcinoma of the supraglottic larynx: a basis for comparing the results of radiotherapy and surgery. Head Neck Surg 1990;12:205)

TABLE 18-20. Supraglottic Carcinoma Treated by Irradiation: Control Above the Clavicles in 129 Patients (No. Controlled/No. Treated)*

Modified AJCC Stage	Excluded*	Control With Initial Treatment	No. Salvaged/ No. Attempted	Ultimate Control
I	2	8/8	No data	8/8
II	3	18/23 (78%)	4/5	22/23 (96%)
III	6	20/34 (59%)	8/10	28/34 (82%)
IVA	0	8/14 (57%)	2/5	10/14 (71%)
IVB	9	13/30 (43%)	4/8	17/30 (57%)

* Excludes 20 patients who died within 2 years of radiotherapy with primary site and neck continuously disease-free. Two patients with synchronous primary lesions were staged according to the most advanced lesion.

(Mendenhall WM, Parsons JT, Stringer SP, Cassisi NJ, Million RR. Carcinoma of the supraglottic larynx: a basis for comparing the results of radiotherapy and surgery. Head Neck Surg 1990;12:208)

TABLE 18-21. Supraglottic Carcinoma Treated by Radiation Therapy: 5-Year Survival in 84 Patients (No. Alive/No. Treated)

Modified AJCC Stage*	Absolute Survival	Cause-Specific Survival
I	2/6	2/2
II	10/20 (50%)	10/12 (83%)
III	9/20 (45%)	9/13 (69%)
IVA	4/9	4/6
IVB	7/29 (24%)	7/22 (32%)

* One patient with synchronous primary lesions was staged according to the more advanced lesion.

(Mendenhall WM, Parsons JT, Stringer SP, Cassisi NJ, Million RR. Carcinoma of the supraglottic larynx: a basis for comparing the results of radiotherapy and surgery. Head Neck 1990;12:208)

TABLE 18-22. Supraglottic Carcinoma Treated by Radiation Therapy: Local Control With Voice Preservation (129 Patients*)

Stage	No. With Local Control and Functional Larynx/No. Treated
T1	14/14 (100%)
T2	46/53 (87%)
T3	33/48 (69%)
T4	8/14 (57%)

* No exclusions; 2 patients with synchronous primaries were staged according to the more advanced lesion. Includes as locally controlled 3 patients successfully salvaged by supraglottic laryngectomy for a local recurrence.

(Mendenhall WM, Parsons JT, Stringer SP, Cassisi NJ, Million RR. Carcinoma of the supraglottic larynx: a basis for comparing the results of radiotherapy and surgery. Head Neck 1990;12:207)

TABLE 18-23. Supraglottic Carcinoma: A Comparison of Surgery and Irradiation—Local Control Following Initial Treatment as a Function of T Stage

T Stage	Irradiation Alone	Surgery ± Adjuvant Irradiation	Level Significance
T1	12/13 (92%)	9/9	.591
T2	29/36 (81%)	20/25 (80%)	.603
T3	12/20 (60%)	17/18 (94%)	.015
T4	4/13 (31%)	15/18 (83%)	.005

Note: 152 patients, 1964–1984 (No. controlled/No. treated).
(Weems DH, Mendenhall WM, Parsons JT, Cassisi NJ, Million RR. Squamous cell carcinoma of the supraglottic larynx treated with surgery and/or radiation therapy. Int J Radiat Oncol Biol Phys 1987;13:1484)

TABLE 18-24. Supraglottic Carcinoma: A Comparison of Surgery and Radiation Therapy—Ultimate Local Control After Salvage Therapy

T Stage	Irradiation Alone	Surgery ± Adjuvant Irradiation	Significance Level
T1	13/13 (100%)	9/9	1.00
T2	32/36 (89%)	21/25 (84%)	.426
T3	15/20 (75%)	18/18 (100%)	.031
T4	7/13 (54%)	15/18 (83%)	.084

Note: 152 patients, 1964–1984 (No. controlled/No. treated).
(Weems DH, Mendenhall WM, Parsons JT, Cassisi NJ, Million RR. Squamous cell carcinoma of the supraglottic larynx treated with surgery and/or radiation therapy. Int J Radiat Oncol Biol Phys 1987;13:1484)

TABLE 18-25. Supraglottic Carcinoma: A Comparison of Surgery and Radiation Therapy—Ultimate Local Control With Voice Preservation

T Stage	Irradiation Alone	Surgery ± Adjuvant Irradiation	Significance Level
T1	15/16 (94%)	8/9	0.600
T2	38/45 (84%)*	12/31 (39%)	<.001
T3	17/25 (68%)	6/26 (23%)	0.002
T4	14/21 (67%)	3/23 (13%)	<.001

* One patient had two T2 primary lesions and was thus counted twice.
Note: 195 patients (No. controlled with voice preservation/No. treated).
(Weems DH, Mendenhall WM, Parsons JT, Cassisi NJ, Million RR. Squamous cell carcinoma of the supraglottic larynx treated with surgery and/or radiation therapy. Int J Radiat Oncol Biol Phys 1987;13:1484)

TABLE 18-26. Supraglottic Carcinoma: A Comparison of Surgery and Irradiation—Control Above the Clavicles After Initial Treatment

Modified AJCC Stage	Irradiation Alone	Surgery ± Adjuvant Irradiation	Significance Level
I	9/10	9/9	.526
II	13/17 (76%)	13/15 (87%)	.392
III	11/18 (61%)	9/10	.116
IVA	7/10	5/11 (45%)	.245
IVB	10/28 (36%)	20/28 (71%)	.008

Note: 156 patients (No. controlled/No. treated).
(Weems DH, Mendenhall WM, Parsons JT, Cassisi NJ, Million RR: Squamous cell carcinoma of the supraglottic larynx treated with surgery and/or radiation therapy. Int J Radiat Oncol Biol Phys 1987;13:1485)

TABLE 18-27. Supraglottic Carcinoma: A Comparison of Surgery and Irradiation—Ultimate Control Above the Clavicles

Modified AJCC Stage	Irradiation Alone	Surgery ± Adjuvant Irradiation	Significance Level
I	10/10	9/9	1.00
II	16/17 (94%)	14/15 (93%)	.726
III	15/18 (83%)	10/10	.249
IVA	8/10	6/11 (55%)	.221
IVB	14/28 (50%)	23/28 (82%)	.012

Note: 156 patients (No. controlled/No. treated).
(Weems DH, Mendenhall WM, Porsons JT, Cossisi NJ, Million RR: Squamous cell corcinoma of the supraglottic larynx treated with surgery and/or radiation theropy. Int J Radiat Oncol Biol Phys 1987;13:1485)

TABLE 18-28. Supraglottic Carcinoma: A Comparison of Surgery and Irradiation—Cause-Specific 5-Year Survival

Modified AJCC Stage	Irradiation Alone	Surgery ± Adjuvant Irradiation	Significance Level
I	6/6	8/8	1.00
II	7/7	8/9	.562
III	3/6	8/8	.055
IVA	4/7	3/7	.500
IVB	5/26 (19%)	11/21 (52%)	.019

Note: 105 patients (No. alive/No. treated).
(Weems DH, Mendenholl WM, Parsons JT, Cassisi NJ, Million RR: Squomous cell carcinomo of the supraglottic lorynx treated with surgery and/or rodiation therapy. Int J Radiat Oncol Biol Phys 1987;13:1485)

TABLE 18-29. Squamous Cell Carcinoma of the Supraglottic Larynx: Absolute Survival Rates* in Patients with Stage IV† Disease

Absolute Survival	Surgery Only‡	Surgery + Radiation Therapy
2 years	39% (34/87)§	69% (37/54)§
5 years	24% (19/78)#	42% (16/38)#

* Living, free of concer.
† Stage IV: T4, N0–N1; T1–T4, N2–N3.
‡ All patients had a total loryngectomy.
§ $P < .005$.
# $P < .08$.

Note: M. D. Anderson Hospitol data; patients treated 1954–1972.
(Fletcher GH, Goepfert H. Lorynx and pyriform sinus. In: Fletcher GH, ed. Textbook of radiotherapy, ed 3. Philodelphia, Lea & Febiger, 1980:357)

TABLE 18-30. Squamous Cell Carcinoma of the Supraglottic Larynx: Active Disease Above the Clavicles after the Initial Surgery (Total Laryngectomy) in Resectable Stage IV Lesions*

Result	Surgery Only	Surgery + Postoperative Radiation Therapy
Definite failure above clavicles (2-year minimum follow-up after rescue surgery, if needed)	24% (28/116)	13% (7/53)

* Stage IV = T4 N0–N1; T1–T4 N2–N3.
(Adopted from Goepfert H, Jesse RH, Fletcher GH, Hamberger A. Optimal treatment for the technically resectable squomous cell carcinoma of the supraglottic larynx. Laryngoscope 1975;85:28)

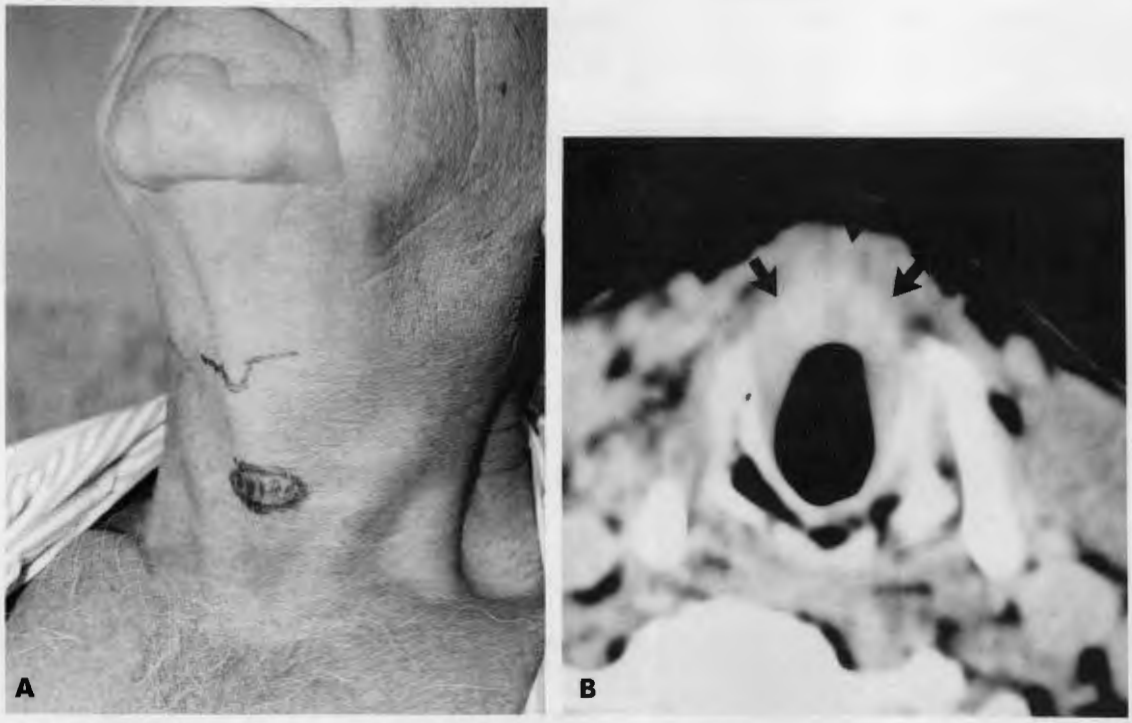

Figure 18-39. Patient was a 74-year-old man with a history of hoarseness. In July 1985, he underwent direct laryngoscopy and biopsy of the right false vocal cord (negative for tumor). His hoarseness persisted, and direct laryngoscopy in September 1985 revealed a granular-lesion in the subglottis that involved the undersurface of both vocal cords. (*A*) A 1×1.5-cm mass, fixed to the cricothyroid membrane, was palpable in the patient's neck. (*B*) CT scan revealed a subglottic tumor (*arrows*) extending through the cricothyroid membrane into the prelaryngeal soft tissues of the neck (stage T4N0M0). The patient underwent a course of radical radiation therapy to 7500 cGy in 63 fractions, 120-cGy twice-daily fractionation, to the primary field, and 4320 cGy in 16 fractions (treatment once daily) to the lower neck. The patient was alive and continuously free of recurrent disease 4 years after irradiation. (Guedea F, Parsons JT, Mendenhall WM, Million RR, Stringer SP, Cassisi NJ. Primary subglottic cancer: results of radical radiation therapy. Int J Radiat Oncol Biol Phys 1991;21:1609)

Results of Treatment

Guedea and associates reviewed six subglottic carcinomas managed by radiation therapy. Clinical stages were carcinoma in situ (one patient), T2N0 (two patients), and T4N0 (three patients). Four were locally controlled for 3½, 4, 4½, and 5 years. Two local failures were treated with salvage laryngectomy, which was successful in one case. Examples of subglottic carcinomas successfully irradiated are shown in Figures 18-39 and 18-40.[26] Warde and coworkers published the largest single series of primary subglottic cancer treated with irradiation alone. They reported local control in 16 of 23 patients (70%). The absolute and cause-specific 5-year survival rates were 26% and 61%, respectively. Twelve patients with T1, T2, or T3 lesions had the disease locally controlled with irradiation, as did 4 of 11 patients (36%) with T4 lesions. Surgical salvage was attempted in 5 patients but was successful in only 1 patient. No long-term complications of irradiation were observed.[85]

Shaha and Shah reported the results of 16 previously untreated patients with primary subglottic cancer treated with surgery (stage I or II, 3 patients; stage III or IV, 13 patients). The cure rate for 13 patients who were eligible for 5-year follow-up was 77% (10/13).[73]

FOLLOW-UP POLICY

Follow-up of patients is planned for every 4 to 6 weeks for 2 years, every 3 months for the third year, and then every 6 months. Photographs are helpful for noting subtle changes. Follow-up by multiple examiners should be encouraged.

The follow-up of patients with vocal cord or supraglottic larynx lesions treated by irradiation or conservation surgery is often more difficult and as important as the treatment itself, since early detection of recurrence usually results in salvage and the salvage may include cure with preservation of voice. It is common to be suspicious of recurrence and yet obtain a negative biopsy at direct laryngoscopy, especially when edema is present; about one third of our patients with local recurrence have negative findings on the first biopsy. Persistent symptoms and abnormal physical findings are an indication to perform another biopsy.

Five patients with early carcinoma of the vocal cord treated by radiation therapy developed a fixed cord but without edema, pain, or other findings to suggest recurrence. Follow-up for several years revealed no evidence of recurrence. Mobility returned after a few weeks to months in three cases.

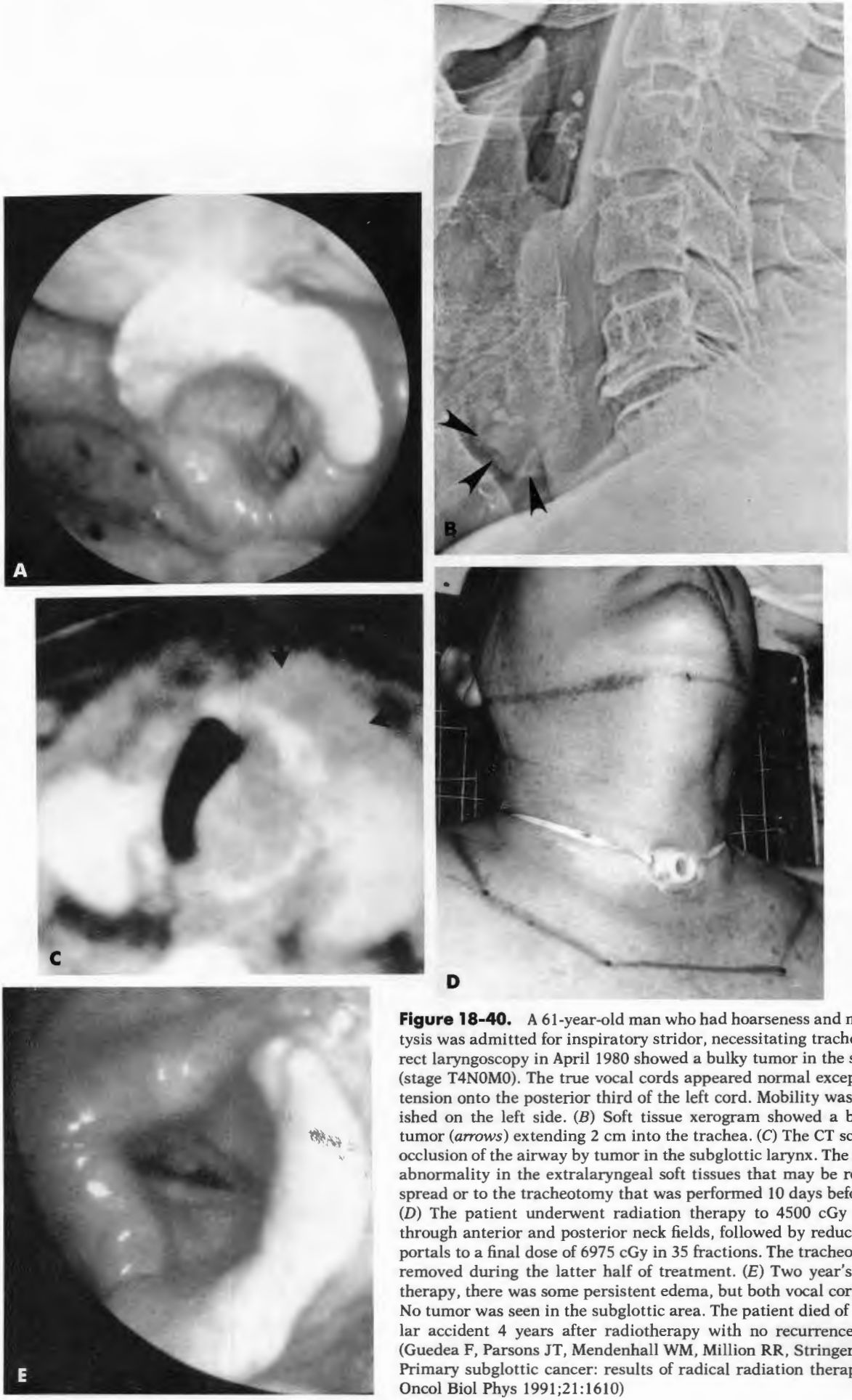

Figure 18-40. A 61-year-old man who had hoarseness and minimal hemoptysis was admitted for inspiratory stridor, necessitating tracheostomy. (*A*) Direct laryngoscopy in April 1980 showed a bulky tumor in the subglottic space (stage T4N0M0). The true vocal cords appeared normal except for tumor extension onto the posterior third of the left cord. Mobility was slightly diminished on the left side. (*B*) Soft tissue xerogram showed a bulky subglottic tumor (*arrows*) extending 2 cm into the trachea. (*C*) The CT scan showed 60% occlusion of the airway by tumor in the subglottic larynx. The arrows show an abnormality in the extralaryngeal soft tissues that may be related to tumor spread or to the tracheotomy that was performed 10 days before the CT scan. (*D*) The patient underwent radiation therapy to 4500 cGy in 24 fractions through anterior and posterior neck fields, followed by reduced lateral boost portals to a final dose of 6975 cGy in 35 fractions. The tracheostomy tube was removed during the latter half of treatment. (*E*) Two year's after radiation therapy, there was some persistent edema, but both vocal cords were mobile. No tumor was seen in the subglottic area. The patient died of a cerebrovascular accident 4 years after radiotherapy with no recurrence of the cancer. (Guedea F, Parsons JT, Mendenhall WM, Million RR, Stringer SP, Cassisi NJ. Primary subglottic cancer: results of radical radiation therapy. Int J Radiat Oncol Biol Phys 1991;21:1610)

When there is suspicion of recurrence and the biopsy result is negative, the patients are reexamined at 2-week intervals until the matter is settled.

Wagenfeld and coworkers studied 740 cases of glottic larynx cancer treated from 1965 to 1974 to determine the incidence of second respiratory tract malignancies.[83] There was a minimum follow-up of 5 years. There were 48 second respiratory tract malignancies, whereas only 14 were expected. Twenty-five were in the lung, and 23 were scattered among other head and neck sites (Table 18-31). Only 7 of the 23 second head and neck primary lesions resulted in death; these second lesions were frequently diagnosed in an early stage during routine follow-up for the glottic lesion.

McDonald and associates reviewed the risk of second malignant tumors in 235 patients treated by radiation therapy for laryngeal cancers. The incidence of lung cancer was 9% and of a new head and neck cancer was 4% with a median follow-up of 10 years.[45] The risks of a second malignancy were similar for glottic and supraglottic carcinomas.

Chest roentgenograms are done twice a year to screen for asymptomatic lung cancer.

Posttreatment Imaging of the Larynx

The evaluation of patients after treatment for head and neck cancer was discussed in Chapter 4. CT and MRI are being studied in the follow-up of patients irradiated for laryngeal cancer. Caution is advised in the interpretation of posttreatment studies to avoid interpreting normal postirradiation changes as recurrent tumor. At worst, this could lead to unnecessary deep biopsies that progress to chondronecrosis and eventually a laryngectomy. We have obtained routine follow-up CT scans at 3- to 6-month intervals for 2 to 3 years after therapy in selected cases at high risk for recurrent tumor. Based on this unpublished experience, it is unusual for CT to detect a recurrence before it is clinically evident.

Imaging reveals consistent and obvious postirradiation changes in the larynx at doses over 6500 cGy. The general changes in the extralaryngeal soft tissues of the neck were discussed in detail in Chapter 6. Mucositis will be seen as superficial, increased signal on T2-weighted MRI and as excessive contrast enhancement on CT. This is mostly observed during and for 6 weeks after therapy. Increased mucosal signal on MRI may persist for many months or years. The endolaryngeal soft tissues virtually always assume a characteristically "boggy" or thickened appearance (see Fig. 18-13). This appearance is usually maximal from the end of therapy to 3 months after therapy. The edema or fibrosis then involutes, but obvious changes persist indefinitely. We have observed persistent, stable thickening of the free margin of the epiglottis, aryepiglottic folds, false cords, posterior walls of the larynx, and pharyngeal walls up to 6 years after radiation therapy. This increased thickness is accompanied by vague increased density in the fat of the preepiglottic and paraglottic spaces as well as the fat within the aryepiglottic folds up to 3 to 6 months after therapy. After 3 to 6 months the fat planes become more distinct, but a vague, increased density is still visible within the deep fat spaces, probably representing fibrosis within this areolar tissue. The intrinsic laryngeal musculature may become atrophic and fat may be replaced, especially on the side of a fixed true cord that does not become mobile after treatment. This atrophy is one possible reason for lack of return of normal function in a successfully treated patient. The subglottic larynx will often show persistent thickening of the mucosa adjacent to the cricoid perichondrium (Fig. 18-41); this is never "normal" in the *untreated* larynx. MRI is no more specific than CT in its rendering of these changes, except that T2-weighted images will reveal edematous mucosa and fat by virtue of its increased water content and high signal. The primary tumor mass gradually involutes during successful radiation therapy, but an obvious focal mass can persist up to 3 months after successful therapy. It is best to avoid imaging until 3 months after therapy so that one is not

TABLE 18-31. Site of Second Primary Respiratory Tract Tumors Among Patients With Glottic Cancer*

Site	No. Tumors	Dead of Second Primary Lesion
Lung	25	23 (92%)
Oral cavity	5	0
Oropharynx	9	1
Hypopharynx	2	2
Nasopharynx	1	1
Antrum	1	1
Esophagus	3	2
Larynx	2	0
Totals	48	30

* Three patients had third respiratory tract primary lesions (1, hypopharynx; 2, lung).

(Wagenfeld DJH, Harwood AR, Bryce DP, van Nostrand AWP, DeBoer G. Second primary respiratory tract malignancies in glottic carcinoma. Cancer 1980;46:1885)

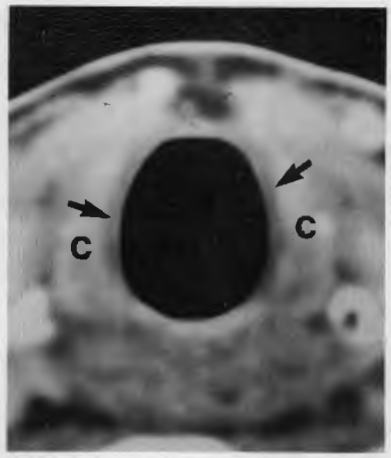

Figure 18-41. Section through the low subglottis in a patient approximately 1 year after the completion of radiotherapy for glottic carcinoma. The symmetric, subtle soft tissue thickening (*arrowheads*) between the inner margin of the cricoid cartilage (C) and subglottic airway is a common finding after radiotherapy. In an untreated patient, this would be definitely abnormal and consistent with some pathologic process of the mucosa or paraglottic space. Other changes in the larynx after radiotherapy are shown in Figure 6-13.

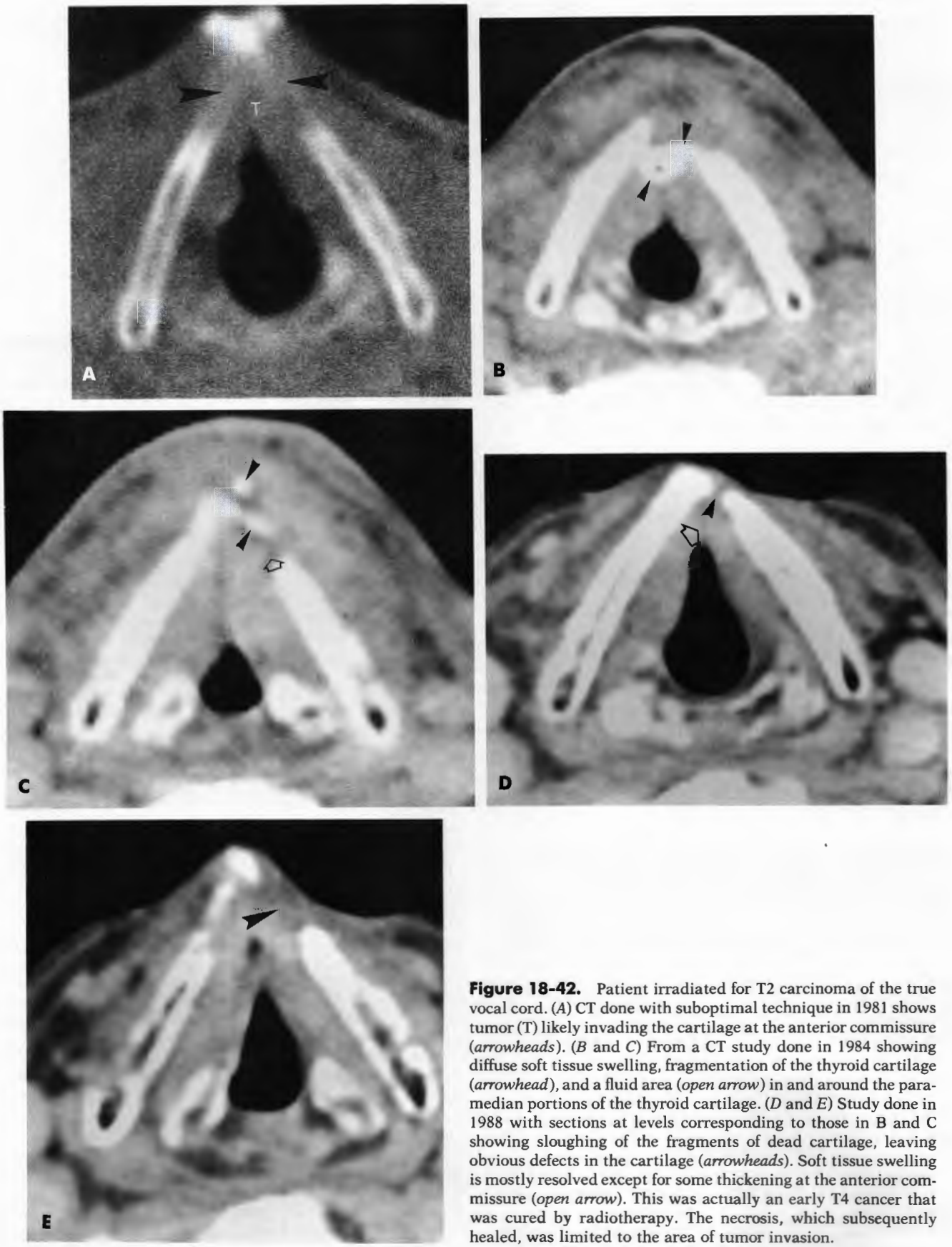

Figure 18-42. Patient irradiated for T2 carcinoma of the true vocal cord. (*A*) CT done with suboptimal technique in 1981 shows tumor (T) likely invading the cartilage at the anterior commissure (*arrowheads*). (*B* and *C*) From a CT study done in 1984 showing diffuse soft tissue swelling, fragmentation of the thyroid cartilage (*arrowhead*), and a fluid area (*open arrow*) in and around the paramedian portions of the thyroid cartilage. (*D* and *E*) Study done in 1988 with sections at levels corresponding to those in B and C showing sloughing of the fragments of dead cartilage, leaving obvious defects in the cartilage (*arrowheads*). Soft tissue swelling is mostly resolved except for some thickening at the anterior commissure (*open arrow*). This was actually an early T4 cancer that was cured by radiotherapy. The necrosis, which subsequently healed, was limited to the area of tumor invasion.

tempted to biopsy the limited areas of CT or MRI abnormality. After 3 months, subtle focal abnormalities should be observed carefully clinically, perhaps with supplemental imaging. *Subtle* residua usually turn out to be sterilized posttreatment scars that remain stable over many years (see Fig. 18-13). Obviously, large or progressively enlarging masses are another matter and usually indicate recurrent tumor.

The patient having either surgery alone or combined treatment may also benefit from follow-up imaging. This is perhaps most difficult in those patients who have had conservation laryngeal surgery. The deformity of the larynx produced by the surgical procedure disturbs the symmetry. Deep-tissue planes such as the paraglottic and preepiglottic spaces are either gone or profoundly altered. Baseline studies should be done in high-risk patients about 3 months postoperatively.

After total laryngectomy or laryngopharyngectomy, baseline studies are usually not necessary, since the reconstructed neopharynx and peristomal region are easy to evaluate. If recurrence develops at the stoma, the stomal site and mediastinum must be studied in detail to determine the level of tracheal involvement, possible spread to the muscular wall of the esophagus, encasement of the aorta or brachiocephalic vessel, mediastinal adenopathy, and pulmonary metastatic disease. MRI is particularly useful for showing tracheal invasion, spread to the muscular wall of the esophagus, paravertebral or prevertebral muscle invasion, vascular encasement, and mediastinal hilar adenopathy. CT is best for detecting nodal disease and pulmonary metastases.

Diagnostic Imaging in Osteochondronecrosis

Radiation-induced osteochondronecrosis is an uncommon complication of radiation therapy. It is often impossible to tell if one is dealing with osteochondronecrosis alone or in combination with recurrence either clinically or with imaging studies. The two situations may co-exist.

Perichondritis and chondronecrosis is manifested first by soft-tissue swelling on CT or MRI. The finding may be focal, for example, if only the arytenoid is involved or more diffuse when both thyroid laminae are involved. The inflammatory swelling will usually be found adjacent to the area of eventual cartilage necrosis. Deep ulcerations containing gas or complete loss of tissue are more advanced soft tissue findings that frequently herald cartilaginous involvement. The inflamed soft tissues will enhance with intravenous contrast medium, and pockets of fluid or abscess-like cavities are frequently visible within or next to dead and dying cartilage.

The affected cartilage may merely become sclerotic. This is typical of arytenoid and cricoid cartilage and may be akin to the changes seen in irradiated bone elsewhere in the body. As the cartilages become weakened, the laryngeal skeleton may begin to collapse, which results in shortening of the cricothyroid and thyrohyoid membrane and ligaments. An "in-bowing" of the thyroid laminae may be the earliest sign of this weakening, and this pattern is especially common if the tumor was located at the anterior commissure (Fig. 18-42). In general, gross necroses of the cartilage tend to occur at points of invasion by tumor, unrecognized or not, before radiation therapy. Late findings, in limited cases, include fragmentation and sloughing of necrotic bone or cartilage leaving obvious defects (see Fig. 18-42). In severe cases, the entire larynx may collapse and fragments (now in reality osteomyelitic sequestra) may lie within areas of gross tissue necrosis. Some cases may heal without serious impairment of the larynx (see Fig. 18-42). Advanced cases may require laryngectomy, especially if the larynx is useless, and there is a concern that coexistent recurrent tumor may be present.

COMPLICATIONS OF TREATMENT

Surgical Treatment

Repeated stripping of the cord for carcinoma in situ or dysplasia may result in a thickened cord and hoarse voice. A thickened cord with hoarseness is also suggestive of submucosal invasive carcinoma. Neel and associates reported a 26% incidence of nonfatal complications for cordectomy (Table 18-32).[55] Immediate postoperative complications included atelectasis and pneumonia, severe subcutaneous emphysema in the neck, bleeding from the tracheotomy site or larynx, wound complications, and airway obstruction requiring tracheotomy. Late complications included removal of granulation tissue by direct laryngoscopy to exclude recurrence, extrusion of cartilage, laryngeal stenosis, obstructing laryngeal web, and several miscellaneous problems.

The postoperative complications and sequelae of hemilaryngectomy include chondritis, wound slough, inadequate glottic closure, and anterior commissure webs. The rate of complications is given in Table 18-33 for 254 patients treated for hemilaryngectomy and for 171 patients treated by total laryngectomy for glottic carcinoma at Washington University School of Medicine, St. Louis.[22] The complications associated with supraglottic laryngectomy and total laryngectomy for supraglottic carcinomas are outlined in Table 18-34.[22] The risk of a complication increased when tumor margins were involved by tumor; there was no change in risk associated with age, sex, race, laryngeal site, stage of primary tumor, size of primary tumor, use of low-dose preoperative irradiation, or status of the positive nodes.

Lee and associates reported the complications for supraglottic laryngectomy, neck dissection, and postopera-

TABLE 18-32. Complications of Laryngofissure-Cordectomy in 182 Patients* (Mayo Clinic)

EARLY	
Cardiac arrest	1
Pulmonary	12
Severe subcutaneous emphysema	4
Wound (eg, bleeding, perichondritis)	10
LATE	
Stenosis or web	3
Cartilage sequestrum	2
Granulation tissue requiring direct laryngoscopy	20
Other	11

* 63 complications in 47 patients (26%).

(Neel HB III, Devine KD, Desanto LW. Laryngofissure and cordectomy for early cordal carcinoma: outcome of 182 patients. Otolaryngol Head Neck Surg 1980;88:83)

TABLE 18-33. Complications of Laryngectomy for Glottic Cancer With and Without Preoperative Irradiation

	Total Laryngectomy		Hemilaryngectomy	
	Without Preoperative Radiation Therapy	With Preoperative Radiation Therapy	Without Preoperative Radiation Therapy	With Preoperative Radiation Therapy
TOTAL NUMBER OF PATIENTS	118*	53*	237†	17†
RESULT				
No complications	85 (72%)‡	36 (68%)	199 (84%)	13 (77%)
Infection	1 (1%)	3 (6%)	1 (<1%)	0
Wound slough	4 (3%)	1 (2%)	2 (1%)	0
Fistula	6 (5%)	1 (2%)	0	0
Hemorrhage	0	2 (4%)	2 (1%)	0
Carotid artery exposure and/or blowout	1 (1%)	0	9 (4%)	1 (6%)
Fatal complication	5 (4%)	0	2 (1%)	0
Other	16 (14%)	10 (19%)	22 (9%)	3 (18%)

* $\chi^2 = 15.934$; $v = 10.07$; $P > .10$.
† $\chi^2 = .712$; $v = 2.62$; $P > .50$.
‡ Number (percent incidence).
Note: Washington University Medical Center, St. Louis, data, 1955–1972.
(Gall AM, Sessions DG, Ogura JH. Complications following surgery for cancer of the larynx and hypopharynx. Cancer 1977;39:626)

tive radiation therapy for bulky intermediate-stage lesions.[42]

Complications included two operative deaths and one late death due to aspiration. Three patients required a complete laryngectomy. About 80% converted to oral feeding by 4 months and 80% were decannulated by 5 months. Nine patients had all or part of one arytenoid removed and had a higher rate of aspiration and greater difficulty with oral feeding.

Radiation Therapy

Glottic Carcinoma

ACUTE COMPLICATIONS. The acute reactions from the treatment of early vocal cord cancer using a tumor dose of 225 cGy per day to a total dose of 5625 cGy to 6300 cGy, five fractions per week, ^{60}Co, and portals measuring 4×4 to 4×5 cm are relatively mild and almost

TABLE 18-34. Complications of Laryngectomy for Supraglottic Cancer With or Without Preoperative Irradiation

	Total Laryngectomy		Supraglottic Laryngectomy	
	Without Preoperative Radiation Therapy	With Preoperative Radiation Therapy	Without Preoperative Radiation Therapy	With Preoperative Radiation Therapy
TOTAL NUMBER OF PATIENTS	37*	25*	39†	94†
RESULT				
No complications	25 (68%)‡	22 (88%)	23 (59%)	67 (71%)
Infection	1 (3%)	0	0	0
Wound slough	0	1 (4%)	1 (3%)	7 (7%)
Fistula	3 (8%)	0	3 (8%)	3 (3%)
Hemorrhage	0	0	1 (3%)	2 (2%)
Carotid artery exposure and/or blowout	1 (3%)	0	2 (5%)	0
Operative death	0	0	1 (3%)	2 (2%)
Fatal complication	0	1 (4%)	1 (3%)	0
Other	7 (19%)	1 (4%)	7 (18%)	13 (14%)

* $\chi^2 = 30.307$; $v = 18.99$; $P < .05$.
† $\chi^2 = 7.769$; $v = 5.20$; $P > .10$.
‡ Number (percentage incidence).
Note: Washington University Medical Center, St. Louis, data, 1955–1972.
(Gall AM, Sessions DG, Ogura JH. Complications following surgery for cancer of the larynx and hypophorynx. Cancer 1977;39:626)

TABLE 18-35. T1–T2 Vocal Cord Carcinoma: Major Irradiation Complications (304 Patients)

Irradiation Technique	Complication Rate
Single, ipsilateral	3/66 (5%)
Parallel opposed, wedges	0/58 (0%)
Three field	2/179 (1%)

(Data from Mendenhall WM, Parsons JT, Million RR, Fletcher GH. T1–T2 squamous cell carcinomo of the glottic larynx treated with rodiation therapy: Relationship of dose-froctionotion factors to local control and complications. Int J Radiat Oncol Biol Phys 1988;15:1267–1273)

never result in a treatment interruption. During the first 2 to 3 weeks, the voice may improve owing to regression of tumor. The voice then generally becomes hoarse, again owing to the radiation-induced changes, even though the tumor continues to regress.

A mild sore throat develops beginning at the end of the second week but uncommonly requires medication. About 50% of patients will develop the sensation of a lump in the throat; this sensation is probably related to some mild edema of the arytenoids and postcricoid area. The patient may associate this "lump" with cancer and should be forewarned.

The voice begins to improve about 3 weeks after completion of treatment, reaching a plateau 2 to 3 months after radiation therapy. The quality and volume of the voice may tend to peter out at the end of the day, and many patients report temporary changes in voice with change in weather and with upper respiratory tract infections. Patients with extensive lesions often recover a normal voice, and an occasional patient with an early lesion will not recover a normal voice, even though the vocal cords may appear normal.

LATE COMPLICATIONS. Edema of the larynx is the most common sequela after irradiation for glottic or supraglottic lesions. The rate of clearance of the edema is related to the dose of radiation, volume of tissue irradiated, addition of a neck dissection, continued use of alcohol and tobacco, and size and extent of the original lesion. For instance, glottic lesions involving the posterior cord require a larger treatment volume and have a slightly higher incidence of edema. Edema may be accentuated by a neck dissection and may require 6 to 12 months to subside.

Soft tissue necrosis leading to chondritis occurs in less than 1% of patients, usually in those who continue to smoke. Soft-tissue and cartilage necroses mimic recurrence, with hoarseness, pain, and edema; a laryngectomy may be recommended in desperation for fear of recurrent cancer.

Corticosteroids such as dexamethasone (Decadron) have been used to reduce edema secondary to radiation effect after recurrence has been ruled out by biopsy. If ulceration and pain occur, administration of an antibiotic such as tetracycline may be of help.

See Chapter 13 for a discussion of chondronecrosis.

Mendenhall and associates reviewed the complications of treatment for 304 patients with T1 and T2 lesions. The risk of a complication was greatest when a single ipsilateral ^{60}Co portal was used (Table 18-35). This technique was discontinued many years ago. The incidence of complications is related to total dose, dose per fraction, and T stage in Table 18-36. The risk was less than 1% for T1 and 3% for T2. Four complications healed with conservative treatment and preservation of the larynx: a chondronecrosis, a subcutaneous fat necrosis, and one temporary and one permanent tracheostomy for laryngeal edema. A fifth patient had a tracheostomy and was then thought to have a recurrence and underwent laryngectomy; there was no tumor in the specimen.[47]

The risk of a complication is related to using a single ipsilateral portal, T2 stage, and high biologic dose (6700 to 7000 cGy at 225 cGy per fraction) (see Table 18-36). With current doses (see Table 18-4) and two- or three-field techniques (see Table 18-35), the rate of complications for patients with T1 or T2 glottic carcinoma is less than 1%.

Supraglottic Carcinoma

ACUTE COMPLICATIONS. During the course of radiation therapy at 180 to 200 cGy per day, the patient will develop a sore throat at the end of the first 2 weeks of

TABLE 18-36. T1–T2 Carcinoma of the Vocal Cord: Incidence of Moderately Severe and Severe Complications—304 Patients* (No. Complications/No. Patients Treated)

	T1		T2		Total	
	Dose Per Fraction		Dose Per Fraction		Dose Per Fraction	
Total Dose (cGy)	225–255 cGy†	185–224 cGy	225–245 cGy‡	175–224 cGy	225–255 cGy	175–224 cGy
>7000	No data	No data	No data	0/3	No data	0/3
6700–7000	No data	0/2	2/7 (29%)	0/12	2/7 (29%)	0/14
6000–6600	0/86	1/58 (2%)	1/61 (2%)	1/34 (3%)	1/147 (<1%)	2/92 (2%)
5400–5700	0/36	0/2	No data	0/2	0/36	0/4

* Patients treated with once-a-day fractionation.

† Only 1 patient was treated at >235 cGy/fraction.

‡ Only 1 patient wos treated at >235 cGy/fraction.

(Mendenhall WM, Parsons JT, Million RR, Fletcher GH. T1–T2 squamous cell carcinoma of the glottic larynx treated with radiation therapy: relationship of dose-fractionation factors to local control and complications. Int J Radiat Oncol Biol Phys 1988;15:1272)

treatment. This will persist until 3 to 4 weeks after completion of treatment. There will be an associated dry mouth from irradiation of the salivary and parotid glands, a loss of taste, and a sensation of a lump in the throat if the entire glottic area is also included. The acute side effects for 120 cGy twice-a-day are similar to those seen with 200 cGy per day.

It is unusual for the patient to require a tracheotomy before irradiation unless airway obstruction develops at the time of direct laryngoscopy and biopsy. In patients who have recovered from the direct laryngoscopy and biopsy without obstruction, we have rarely had to do a tracheotomy during the fractionated course of radiation therapy. Significant regression of the partially obstructing tumor usually occurs within the first 2 weeks, before the edema begins, and the tracheotomy is avoided.

Examples of acute chondritis requiring discontinuation of treatment have not been seen, even though almost all the epiglottic lesions, either suprahyoid or infrahyoid, have cartilage invasion. The radiation reaction normally subsides 3 to 5 weeks after completion of treatment, and simultaneously the sore throat disappears. The patient recovers over the next weeks or months. The dryness is rarely severe, since there is protection of part of the major salivary glands.

LATE COMPLICATIONS. The most common sequela of radiation therapy is temporary lymphedema.

The epiglottis, both suprahyoid and infrahyoid portions, will remain thicker than normal for periods of time, but this thickening is not often associated with difficulty in swallowing, respiratory obstruction, or aspiration. Lesions of the suprahyoid epiglottis frequently destroy the tip of the epiglottis, and this may require some time for the exposed cartilage to heal (see Color Fig. 7 in Chap. 3).

Successful irradiation of infrahyoid epiglottic tumors is not associated with a high rate of necrosis, even though almost all of these lesions penetrate the porous epiglottic cartilage. Examination of the epiglottis after radiation therapy is sometimes difficult because of the edema, but the fiberoptic laryngoscope allows nearly everyone to be examined. Shukovsky analyzed the risk of severe complications for 114 patients with squamous cell carcinoma of the supraglottic larynx.[74] There were 5 patients who developed a necrosis and 7 patients who developed severe edema. All but one of these complications appeared with doses in excess of 7000 cGy over 7 weeks or with a larger treatment volume.

Mendenhall reviewed the complications occurring in 129 patients managed by continuous-course radiation therapy, with or without neck dissection. Table 18-37 shows the incidence of severe complications and Table 18-38 lists the nine complications (Mendenhall WM, written communication, April 1989). The immediate mortality from irradiation effects was 2 of 129 (2%). Two patients with T4 lesions developed chondronecrosis leading to a total laryngectomy in one and a permanent tracheostomy in the other. All of the complications resulting in total laryngectomy or permanent tracheostomies occurred in patients who would have required a total laryngectomy.

Complications With Twice-a-Day Fractionation

Parsons reviewed the severe complications for 74 patients with supraglottic carcinoma managed by 120 cGy twice-a-day (Parsons JT, personal communication, March 1990). The rate of complications was T1, 0/2; T2, 1/20; T3, 1/50; and T4, 1/2. One laryngeal necrosis was fatal. None of the three patients with severe complications was suitable for conservation laryngectomy. There were no complications at total doses of 7440 cGy, but the risk goes up quickly with higher T stages and doses of 7680 cGy or greater.

TABLE 18-37. Supraglottic Larynx Carcinoma Treated With Radiation Therapy ± Neck Dissection*—Severe Complications According to T Stage (129 Patients)

Stage	Incidence
T1	0/14
T2–T3	4/101 (4%)
T4	4/14 (29%)

* Continuous-course radiation therapy.
Note: University of Florida data; patients treated October 1964 to April 1987; analysis April 1989 by W. M. Mendenhall.

Parsons and coworkers detailed the complications for 21 T3 glottic lesions managed by 120 cGy twice-a-day fractionation, 7440 to 7920 cGy.[62] Mild to moderate lymphedema is common for 6 to 12 months and gradually resolves; none of the cured patients required a tracheostomy. One patient developed a cervical esophageal stricture that required three dilatations; the patient remains free of disease more than 5 years after treatment, on a liquid diet. Another patient had eight deep negative laryngeal biopsies 6 weeks after radiation therapy. The larynx never healed and laryngectomy at 5 months was free of tumor; the patient is free of disease at 7 years. Temporary pharyngocutaneous fistula occurred in four of six patients after salvage laryngectomy.

A steep dose–response curve for laryngeal complications has been demonstrated in the University of Florida experience with twice-a-day fractionation.[63] One hundred fifty-seven patients with cancer of the larynx (glottic or supraglottic) and 60 patients with carcinoma of the pharyngeal wall and pyriform sinus were treated be-

TABLE 18-38. Supraglottic Larynx Carcinoma Treated With Radiotherapy ± Neck Dissection* (129 Patients): Severe Complications

Complications	No. Complications
Laryngeal edema requiring tracheostomy	3†
Chondronecrosis	2‡
Partial spinal cord transection	1
Soft tissue necrosis pharyngeal wall	1 (1 fatal)
Aspiration pneumonia	1 (1 fatal)
Total	9 in 9 patients

* Continuous-course radiation therapy.
† Two of three tracheostomies were permanent.
‡ One of two required total laryngectomy.
Note: University of Florida data; patients treated October 1964 to April 1989; analysis April 1989 by W. M. Mendenhall.

TABLE 18-39. Supraglottic Carcinoma (195 Patients): Incidence of Severe Complications

Initial Treatment	No. Patients With Severe Complications/ No. Initially Treated	No. Patients With Severe Complications/ No. Attempted Salvage Procedures
Irradiation alone	5/106 (5%)	2/20 (10%)
Surgery alone	6/26 (23%)	1/4
Preoperative irradiation + surgery	6/28 (21%)	0/1
Surgery + postoperative irradiation	6/35 (17%)	1/4

(Weems DH, Mendenhall WM, Parsons JT, Cassisi NJ, Million RR. Squamous cell carcinoma of the supraglottic larynx treated with surgery and/or radiation therapy. Int J Radiat Oncol Biol Phys 1987;13:1485)

tween 1978 and 1989. There was one moderate complication observed in 100 patients who received a larynx dose of 7440 cGy, and four moderate and seven severe complications in 99 patients who received a larynx dose of 7680 cGy. Part of the rapid increase in complications over the small dose increment was due to the use of higher doses in more advanced cases.

Salvage Laryngectomy

Total laryngectomy for T1 and T2 lesions recurrent after irradiation is relatively free of serious complications. Total laryngectomy for T3 or T4 lesions recurrent after high-dose irradiation is associated with major morbidity in about one third of patients, including pharyngocutaneous fistula and wound dehiscence.

Combined Treatment

Most surgeons agree that preoperative irradiation is generally associated with an increased risk of an operative complication and slightly prolonged hospitalization. If the same goal can be accomplished by postoperative irradiation, the overall complication rates are lower.

Weems and coworkers presented the incidence of severe complications according to the initial treatment (Table 18-39). There was one fatal carotid rupture in the preoperative group. There was one instance of fatal carotid rupture in the postoperative group and one case of severe edema after supraglottic laryngectomy that required a tracheostomy. Although the rate of surgical complications is similar among the three treated groups, the severity of the complications and the fatality rate is greater with combined therapies.[86]

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19

SPEECH REHABILITATION AFTER TOTAL LARYNGECTOMY

LEWIS P. GOLDSTEIN AND GERALD E. MERWIN

Those patients whose disease dictates complete laryngectomy are left voiceless, but not necessarily speechless. Overcoming cancer and restoring communication skills require early interaction and team planning among the patient, family, physicians, and speech pathologists.

There are four methods by which alaryngeal voice is produced: (1) intrinsic (buccal, pharyngeal, and esophageal); (2) prosthetic (artificial larynx); (3) surgical (tracheoesophageal fistula, "neoglottis"); and (4) surgical-prosthetic (pharyngotomy with prosthesis, tracheoesophageal fistula with valve). Each of these methods has specific applications with attendant advantages and disadvantages.

In choosing the best method for voice rehabilitation, one must consider that any given patient may be capable of using one or more methods. There is no proof to support the once widely held view that learning or using one method of speaking is detrimental to learning or using another method. The authors offer an electronic artificial larynx to all patients when they have sufficiently recovered from the laryngectomy, usually within 10 days. In patients who have not had voicing procedures done at the time of primary surgery, esophageal speech training begins approximately 3 weeks after surgery. After no more than 3 months, patients are evaluated and consideration is given to potential surgical-prosthetic approaches to voice restoration. It is not unusual for patients to speak mainly with a tracheoesophageal puncture and valve, using esophageal speech for short utterances, but still relying on an electronic artificial larynx when fatigued or experiencing respiratory difficulties.

Decisions regarding which method or methods are appropriate for a given patient are made jointly by the team after considerable teaching and counseling are provided for the family and patient by the speech pathologist and physician. The extent of surgery and the skills and communication needs of the patient should be considered.

INTRINSIC SPEECH DEVELOPMENT

After laryngectomy, the patient is capable of producing sound without the need for surgery and without a prosthetic device, using only the anatomy he or she possesses intrinsically. The three intrinsic methods are buccal, pharyngeal, and esophageal. Buccal speech consists of moving the air between the cheeks, tongue, and palate to produce sound. This results in a "Donald Duck" form of speech. Pharyngeal speech is produced by trapping air in the back of the throat. Vibration of the pharyngeal tissue produces a high-frequency, squeaky sound. Both of these methods yield poorly intelligible speech and are considered undesirable methods of communication.

In the past, esophageal speech has been a major intrinsic form of oral communication after laryngectomy. Production of an esophageal voice consists of using the esophagus as a pseudolung and the pharyngoesophageal segment as the vibrating source. The esophageal speaker must produce a pressure decrease across the pharyngoesophageal segment to achieve insufflation of air into the esophagus. The speaker must also develop a pressure differential across the pseudoglottis to drive it into oscillation.

Snidecor and Curry[24,25] described various characteristics of esophageal speech. Evaluation of the speech of six superior esophageal speakers revealed the following:

- The mean fundamental frequency of male esophageal speakers was 65 Hz, approximately one full octave below that of normal male speakers.
- Pitch variability was comparable to that produced in normal speech.

Superior esophageal speakers averaged between 85 and 129 words per minute.
Superior esophageal speakers averaged 5 words per air charge, whereas normal speakers average 12½ words per breath.

Only a limited percentage (less than 10%) of patients achieve a level of acceptable esophageal speech.

PROSTHETIC ARTIFICIAL LARYNX

Many types of artificial larynxes are available. They vary by their power source, pneumatic or electronic, and their site of placement, intraoral or transcervical.

The Cooper-Rand is an intraoral electronic device. It consists of a battery-powered tone generator that places the sound directly into the oral cavity through an air-filled tube (Fig. 19-1).[4] A transcervical device (Servox) consists of a battery-powered vibrating head that, when coupled with neck tissue, transfers the sound into the pharynx and then the oral cavity for articulation (Fig. 19-2).[4] Devices vary primarily in the manner used to produce sound.

The quality of sound, ease of use, and other physical characteristics vary greatly from device to device. The electronic hand-held artificial larynx requires inclusion of the arm, hand, and thumb in the speech circuitry to properly position the device and coordinate voicing (pressing the "on" button) and articulation. The person's ability to use a device, the extent of surgery, and the amount of training, as well as many other variables, make the output of the same device different from patient to patient. These factors determine which device, if any, is best suited to the individual patient. There have been numerous studies pertaining to listeners' judgments of artificial larynx speech, as compared with other forms of speech. In all studies that compared normal speech with alaryngeal speech, normal laryngeal speech was always found to be easily differentiated and superior.[3,7,11,15] In comparing these and other studies, it is evident that no matter which parameter is being judged (intelligibility, preference, acceptability, or proficiency), the results are conflicting and more dependent on the speaking ability of the alaryngeal speaker than on the sound source. In an attempt to determine which variables are important for good artificial larynx speech production, Goldstein and Rothman[9] compared and analyzed the speech of five poor artificial larynx speakers and five good artificial larynx speakers. Rate of speaking, intensity range, and frequency range were the three factors that differentiated significantly between the two groups. The good speakers spoke at a faster rate and achieved a wider range of intensity and frequency changes while speaking.

Salmon[19] and Goldstein,[8] in discussing the artificial larynx, make the following general points:

- Artificial larynx devices should be introduced early in the patient's speech rehabilitation program.
- Artificial larynx devices should be selected for individual use based on the patient's needs, skills, preferences, and limitations.
- Artificial larynx speech should be used initially and continued in conjunction with esophageal speech training.
- Artificial larynx speech is acceptable, and the patient has the right to choose how he or she will incorporate its use with other forms of alaryngeal communication.
- Artificial larynx speech is intelligible if properly taught and used.

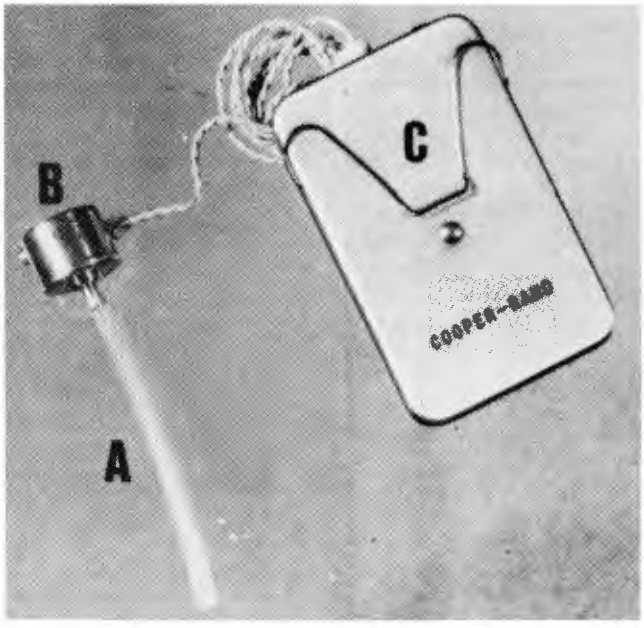

Figure 19-1. Cooper-Rand electronic larynx. A, mouth tube; B, hand-held tone generator; C, pulse generator and battery case. (Blom ED. The artificial larynx: past and present. In: Salmon S, Goldstein LP, eds. The artificial larynx handbook. New York, Grune & Stratton, 1978:67)

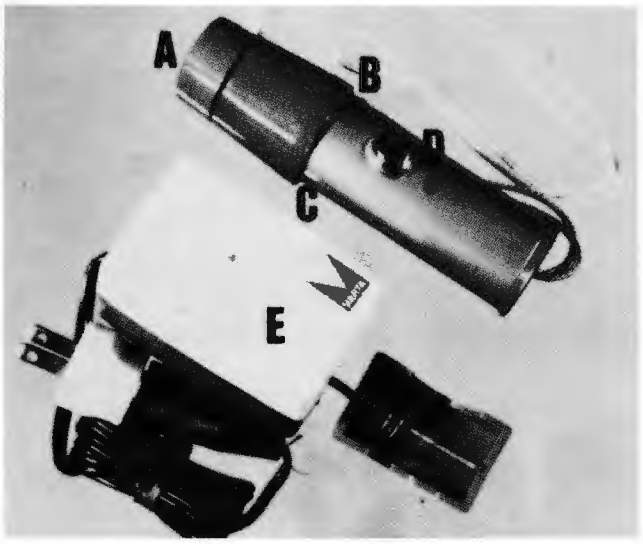

Figure 19-2. Servox electronic larynx. A, vibrator mechanism; B, pitch control; C, volume control; D, on-off switch; E, battery charger. (Blom ED. The artificial larynx: past and present. In: Salmon SJ, Goldstein LP, eds. The artificial larynx handbook. New York, Grune & Stratton, 1978:78)

SURGICAL SPEECH DEVELOPMENT

Restoration of voice after laryngectomy by surgically creating a fistula from the pulmonary power source by way of the trachea to a potential vibratory source, the pharyngoesophageal segment, dates back to the first laryngectomy.[10] Throughout the history of surgical restoration of voice, the advantages of lung-powered speech have come at the cost of aspiration. In most early attempts, a passageway was created from the pharynx to the trachea. Various techniques and tissues were used for this passageway, including anterior esophageal mucosa, vein, skin tube, and tracheal tube with side-to-side anastomosis.[1,2,5,6,14,18] Although unacceptable aspiration was the primary problem, recurrent stenosis of the tract also occurred. When this type of fistula failed, the patient had to undergo corrective surgery. Because of these problems, techniques of this type have not had continued use.

Tracheohypopharyngeal fistula voice with control of aspiration was reported by Staffieri.[26] This surgical technique is employed at the time of primary surgery and requires a high tracheal resection at a point from the cricoid cartilage to the second tracheal ring. In a sense, this represents less than a widefield laryngectomy, and it is not adequate for laryngeal tumors with subglottic or pharyngeal involvement. This technique is rarely used today.

SURGICAL-PROSTHETIC SPEECH DEVELOPMENT

Surgical-prosthetic approaches have been designed to produce speech using a pulmonary air power source; either an external or internal prosthesis is employed to connect the air source to the vocal tract. Three methods using an external prosthesis have been used but have had limited application. Two methods using internal prostheses have been introduced and appear to offer simple, efficient options.

Internal Prosthesis

Singer and Blom[21] introduced a surgical-prosthetic approach to alaryngeal communication that combines a low-morbidity endoscopic procedure with an internal "duck bill" type of valve. A tracheoesophageal fistula, similar to the side-to-side fistula of Amatsu and coworkers,[1] is created by a simple puncture technique. Once a fistula has been created, a silicone-rubber prosthesis is placed in the fistula tract (Fig. 19-3). Similar in shape to the end segment of a rubber catheter, the prosthesis has a slit in the esophageal end to allow air flow while preventing aspiration. The tracheostoma must be covered to divert air to the esophagus and pharyngoesophageal segment for voice production. Aspiration

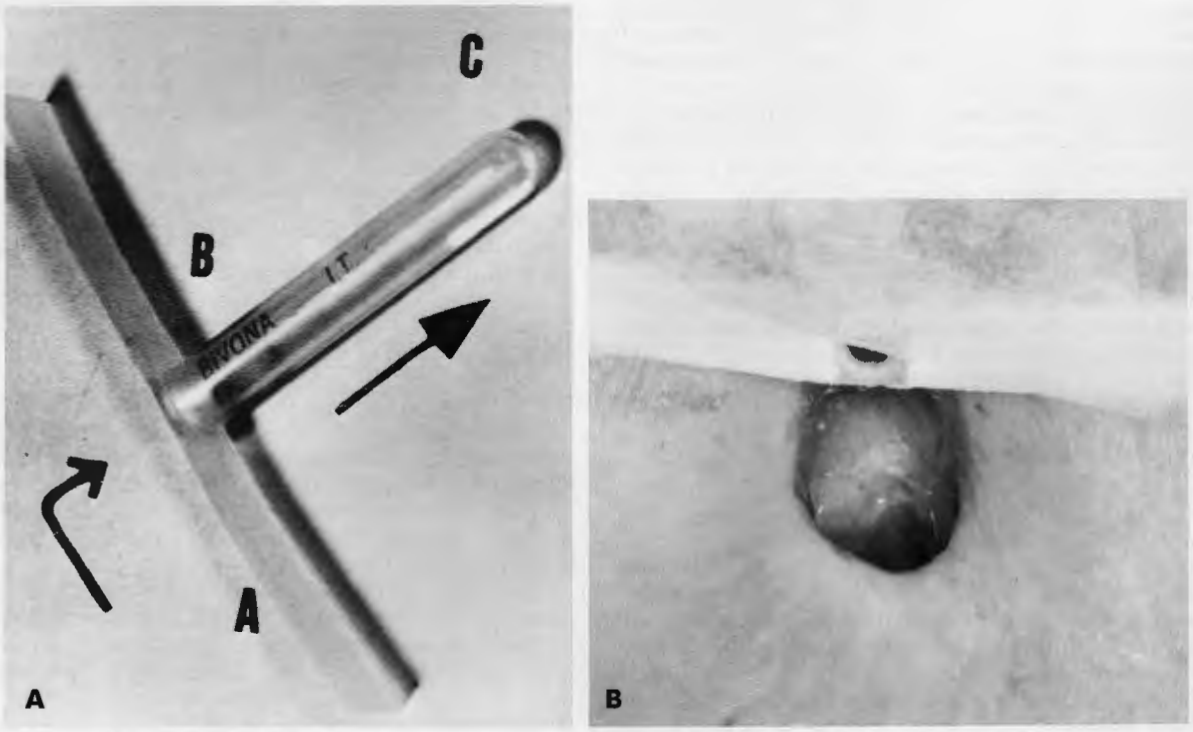

Figure 19-3. (*A*) Duck bill prosthesis. Flange (A) is taped to the skin. Arrows show direction of air flow through shaft (B). The rounded end of the duck bill valve (C) is bivalved and rests in the esophagus. There are recent modifications to assist in securing the shaft in place. (*B*) Duck bill taped in place.

and stenosis are entirely prevented while the prosthesis is in place. The prosthesis must be cleaned regularly and replaced at intervals of 2 to 4 months. Functional speech is achieved in 70% to 85% of properly evaluated patients.[13,23,29,30] Speech using the Blom-Singer prosthesis closely resembles superior esophageal speech acoustically and normal speech in rate; such speech is preferred over artificial larynx speech.[17]

Few limitations are placed on the selection of patients for whom this technique may be used. The stoma must be no less than 1.5 cm in diameter, and the back wall of the trachea must be accessible for placement of the prosthesis 3 to 4 mm below the myocutaneous junction. Hypopharyngeal constrictor muscle spasm can prevent passage of air through the pharyngoesophageal segment in some patients. This may be corrected with myotomy.[22] Laryngopharyngoesophagectomy patients with reconstruction using microvascular free tissue grafts,[28] visceral transposition, myocutaneous flaps, and cervical flaps[16] can be successfully rehabilitated with this technique, but with a much lower success rate.

Provision of primary voice restoration at the time of laryngectomy has become a practical method. Complications encountered include tracheoesophageal fistula closure, postoperative fistula, stomal stenosis, granulation at the tracheoesophageal fistula site, and aspiration of prosthesis. None of these complications, if adequately managed, precludes voice restoration. Primary voice restoration technique is cost-effective because it eliminates a secondary procedure; the puncture site can be used for postoperative enteral nutrition, thereby eliminating the need for a nasogastric tube; and, finally, early voice production gives the patient a psychological boost, which undoubtedly improves convalescence.[27,31] Further developments of the Blom-Singer prosthesis include a low-pressure prosthesis that incorporates an internalized one-way valve. This device produces minimal resistance, greatly reducing the relative effort required to shunt pulmonary air through the prosthesis for speech production. To enhance alaryngeal speech, a tracheostoma breathing valve is available. This valve is placed over the stoma and voice prosthesis, allowing the patient to produce speech without digital occlusion. The valve remains open during normal breathing and closes with increased pulmonary airflow (Fig. 19-4). The tracheostoma breathing valve is composed of a flexible circular housing and a sensitive airflow diaphragm assembly that is inserted into the housing. The housing adheres to the stoma with both double-faced tape and liquid adhesive or a custom fitting as shown in Figure 19-4.

Figure 19-4. Tracheostoma breathing valve with customized flexible mold.

Surgical Considerations

Planning for alaryngeal speech rehabilitation should be included when consideration is given to plans for treatment of the primary disease. Reconstruction of the hypopharynx must be accomplished without undue constriction or scarring to allow unrestricted swallowing and flow of tracheoesophageal air for voice production. A posterior myotomy may be performed or the anterior constrictor muscles are not closed at the time of surgery to prevent stenosis. Particular care and attention must be devoted to creating the tracheostoma. The stoma should be of sufficient size to allow proper ventilation and possible future insertion of a prosthesis. The tracheal stump should be properly beveled so that the cut end of the posterior tracheal wall lies in the plane of the anterior neck skin, and the parastomal contour should be flat and flush with the beveled end of the trachea, which allows the option of future internal valve placement and proper fitting for a stomal cover or valve. Taking time to observe these reconstructive techniques provides the widest possible range of rehabilitative options.

The tracheoesophageal puncture procedure is not complex; however, the potential for complications exists. These include mediastinitis and sepsis, and cellulitis about the puncture site. Major complications are rare.[20] Radiation therapy, whether preoperative or postoperative, does not preclude using this technique. During the period of irradiation, speech may be affected and reactivity at the fistula may occur; however, ultimate success with alaryngeal speech is not diminished.[12]

APPROACH TO COUNSELING

For the patient and family, the diagnosis of "cancer of the voice box" engenders a multitude of fears. In addition to the fear of cancer and all the emotions that word might elicit, there is the fear of major, life-threatening surgery, the fear of loss of speech and the ability to communicate, and the fear of becoming a social and psychological burden.

The objective of preoperative counseling by a speech pathologist is to assure the patient that, although he will be voiceless as a result of the removal of the larynx, he need not be speechless. As the speech pathologist outlines the rehabilitative program, each of the alaryngeal speech methods should be described and demonstrated. It is also beneficial to have the patient visited by an experienced alaryngeal speaker. The patient should be given reading material aimed at answering questions about this condition (available from the American Cancer Soci-

ety). The patient's present speech pattern is recorded and analyzed so that the rate of speech, phrasing, and articulation can be integrated into alaryngeal speech rehabilitation.

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HYPOPHARYNX: PHARYNGEAL WALLS, PYRIFORM SINUS, POSTCRICOID PHARYNX

RODNEY R. MILLION, NICHOLAS J. CASSISI, AND ANTHONY A. MANCUSO

The term *hypopharynx* ("low pharynx") refers arbitrarily to that portion of the pharynx from the level of the hyoid bone (ie, the base of the vallecula and pharyngoepiglottic folds) to the beginning of the esophagus at the plane of the lower border of the cricoid cartilage. The posterior and lateral oropharyngeal and hypopharyngeal walls are continuous, however, and are considered together in this chapter, since there is no distinct difference in the presentation, treatment, or prognosis of lesions of these structures. The great majority of hypopharyngeal lesions originate in the pyriform sinus. Postcricoid carcinomas are fortunately uncommon in the United States.

ANATOMY

The epithelium of the pharyngeal mucous membrane is squamous. It is continuous above with the mucous membrane of the nasopharynx; there is no visible point or line of transition. The dividing point between the nasopharynx and posterior oropharyngeal wall is actually Passavant's ridge, a sphincter-like zone of the superior pharyngeal constrictor that contracts to close the nasopharynx during swallowing. Beneath the mucous membrane of the posterior and lateral walls are the thin constrictor muscles. Between the constrictor muscles and the prevertebral fascia that covers the longitudinal spinous muscles (longus colli and longus capitis) is a thin layer of loose areolar tissue, the retropharyngeal space. The entire thickness of the posterior pharyngeal wall from the surface of the mucous membrane to the vertebral body is no more than 1 cm in the midline. Lateral to the pharyngeal wall are the vessels, nerves, and muscles of the parapharyngeal space (see Fig. 17-2 in Chap. 17). The constrictor muscles are relatively thin, especially the superior constrictor, and do not present much of an obstacle to tumor penetration. There is a variable weak spot in the lateral pharyngeal wall just below the hyoid where the middle and inferior constrictor muscles fail to overlap. The lateral wall in this area is composed of the thin, fibrous thyrohyoid membrane, which is penetrated by the vessels, nerves, and lymphatics of the laryngopharynx (see Fig. 18-3 in Chap. 18).

The pharyngeal walls are continuous with the cervical esophagus below. The hypopharyngeal walls are visible by indirect mirror examination. The transition to cervical esophagus is below the arytenoids and invisible to mirror examination; the transition zone, 3 to 4 cm in length, is referred to as the postcricoid pharynx and is dealt with separately, since tumors of this area present a special clinical picture.

The lateral pharyngeal wall is a narrow, ill-defined strip of mucosa. It lies behind the posterior tonsillar pillar in the oropharynx; it is partially interrupted by the pharyngoepiglottic fold and then continues into the hypopharynx, where it becomes the lateral wall of the pyriform sinus. The lateral pharyngeal wall has a maximum width of 2 cm at any point. The superior horn of the thyroid cartilage may protrude into the lateral pharyngeal wall on one or both sides, producing a submucosal bulge. The posterior pharyngeal wall is 4 to 5 cm wide and 6 to 7 cm high. Submucosal bulges may be seen due to osteophytes on the anterior lips of the cervical vertebrae or the carotid artery and may be mistaken for a submucosal tumor.

The pyriform ("pear shaped") sinus is created by the intrusion of the larynx into the anterior aspect of the

pharynx. This creates pharyngeal grooves lateral to the larynx. The superior margin of the pyriform sinus is the pharyngoepiglottic fold and the free margin of the aryepiglottic fold. The superolateral margin of the pyriform sinus is considered to be an oblique line along the lateral pharyngeal wall just opposite the aryepiglottic fold. The pyriform sinus therefore is made up of three walls, the anterior, lateral, and medial; posteriorly, the pyriform sinus is continuous with the pharyngeal cavity. The pyriform sinus tapers inferiorly to the apex and usually terminates between a level with the top of the cricoid cartilage to just below the lower border of the cricoid. The superior limit of the pyriform sinus is opposite the hyoid. The thyrohyoid membrane is lateral to the upper portion of the pyriform sinus (membranous pyriform sinus), and the thyroid cartilage is lateral to the lower portion (cartilaginous pyriform sinus). The cricoid lamina and the cricoarytenoid joint and muscles lie medial to the pyriform sinus. The internal branch of the superior laryngeal nerve lies in the anterior wall of the pyriform sinus and is said to produce a mucosal fold, but we have been unable to detect this often-described normal anatomy. The pathway for referred pain to the external auditory canal by way of the auricular branch of the vagus nerve is shown in Figure 16-16 in Chapter 16. The auricular branch is sensory to the skin of the back of the pinna and the posterior wall of the external auditory canal. Patients with referred pain from the larynx or hypopharynx will often point behind the ear and generally are vague about the location of the earache. (See the section on anatomy in Chapter 18 for further details about anatomic relationships between the larynx and pyriform sinuses.)

The postcricoid pharynx is funnel-shaped to direct food into the esophagus. There is no discrete superior margin, but it may be considered to begin just below the arytenoids. The anterior wall is the mucosa on the posterior aspect of the cricoid cartilage and is therefore also the posterior wall of the lower larynx; this wall is sometimes referred to as the "party wall." The posterior wall is merely a continuation of the hypopharyngeal walls and is formed by the inferior constrictor muscle. The recurrent laryngeal nerve lies between the lateral wall and the deep surface of the thyroid gland. At the junction of the pharynx with the cervical esophagus, the muscular wall consists of the inferior constrictor muscle and is incomplete posteriorly; this represents the site of herniation to form an esophageal diverticulum.

PATHOLOGY

Over 95% of malignant tumors are squamous cell carcinomas or one of the variants. Carcinoma in situ is commonly seen in surgical specimens at the edge of neoplasms of the pharyngeal wall, and multifocal skip areas of carcinoma in situ may make it difficult to obtain clear margins if excision is done. Minor salivary gland tumors are rare.

PATTERNS OF SPREAD

Posterior Pharyngeal Wall

Carcinomas of the posterior pharyngeal wall have a natural tendency to remain on the posterior wall, grow up or down the wall, and infiltrate posteriorly; they may spread circumferentially to the lateral walls when advanced. Early lesions are red and sometimes have white patches sprinkled over the involved area. The uncommon early lesion (1 to 2 cm) may be exophytic. As the lesion progresses, the tumor enlarges submucosally and bulges into the pharyngeal cavity, and a ragged, midline, linear ulceration appears. The posterior tonsillar pillars may become involved, with spread up the pillars eventually reaching the palate. Advanced lesions have a tendency to terminate inferiorly at the level of the arytenoids without spreading into the postcricoid region. Superiorly they may extend into the nasopharynx. Direct invasion of the prevertebral space, cervical vertebrae, or base of the skull is uncommon.

Lateral Pharyngeal Wall

The lateral pharyngeal wall (including both the lateral oropharyngeal wall and the lateral hypopharyngeal wall) is a rather limited, ill-defined area, and only a few early lesions can be specifically designated to this site. Early tumors may be well-defined exophytic lesions. As they advance, they have a tendency to lateral penetration through the constrictor muscle and thyrohyoid membrane, thus entering the lateral pharyngeal space or the soft tissues of the neck to involve the neurovascular bundle. The direct extension may form a mass and be palpable in the neck just below the hyoid and be confused with a lymph node. The muscles of the pharynx originate from the base of the skull, eustachian tube, styloid process, pterygomandibular raphe, and hyoid bone; and tumor may spread along muscle and fascial planes to all muscular points of origin.[2] Tumor also courses along the glossopharyngeal and vagus nerves and the sympathetic chain. The thyroid gland is adjacent to the lower walls and is often invaded. Tumor secondarily invades the pharyngoepiglottic fold, the vallecula, and the anterior and lateral walls of the pyriform sinus.

Pyriform Sinus

Early lesions usually appear as nodular mucosal irregularities. Submucosal spread is a characteristic feature, with tumor often found more than 1 cm beyond the obvious tumor edge.

Medial wall lesions may extend superficially to involve the mucosa of the aryepiglottic fold and arytenoids or may invade directly into the false cord and aryepiglottic fold. They also grow posteriorly to the postcricoid region and extend to the opposite pyriform sinus. The vocal cord becomes fixed owing to infiltration of the cricoarytenoid muscles, the cricoarytenoid joint, the thyroarytenoid muscles (vocalis muscle), or, rarely, the recurrent laryngeal nerve. They penetrate toward the paraglottic and preepiglottic fat spaces (see section on anatomy in Chap. 18) and then grow inferiorly along the inner face of the thyroid cartilage toward the cricothyroid membrane. Spread into the cervical esophagus is a late event.

Lesions arising on the lateral wall tend toward early invasion of the posterior thyroid cartilage and the posterosuperior cricoid cartilage. The ipsilateral superior lobe of the thyroid gland may be invaded after tumor

penetrates the cartilage, but thyroid invasion occurs without cartilage invasion when tumor penetrates behind the thyroid cartilage or through the cricothyroid membrane. Kirchner reports that thyroid cartilage invasion is associated with involvement of the apex of the pyriform sinus and the extent of invasion cannot be predicted on the basis of visible disease.[8] Lesions of the lateral walls tend to spread submucosally onto the posterior pharyngeal wall. It is often difficult to estimate the extent of postcricoid invasion except at direct laryngoscopy, since these areas are impossible to visualize indirectly. Even with direct endoscopy, invasion is probably often underestimated.

Advanced lesions of the pyriform sinus invade all three walls, fix the larynx, involve the ipsilateral posterior pharyngeal wall, invade the thyroid cartilage and thyroid gland, affect the base of the tongue, and often escape into the soft tissues of the neck. The preepiglottic space is often involved. Perineural invasion of the recurrent laryngeal nerve may be seen in whole-organ sections.

Postcricoid Pharynx

Early lesions of the postcricoid area are rarely diagnosed. Lesions arising from the posterior wall tend to remain on the posterior wall. Lesions arising from the anterior wall tend to invade the posterior cricoarytenoid muscle and the cricoid and arytenoid cartilages. Advanced tumors eventually encircle the lumen. Since the apex of the pyriform sinus terminates in the postcricoid area, some lesions secondarily invade the apex of the pyriform sinus early.

Lymphatics

Oropharyngeal Walls

The distribution and N staging on admission before treatment for 149 previously untreated patients with squamous cell carcinoma arising from the oropharyngeal walls are shown in Figure 20-1*A*; the majority of these lesions occur on the posterior pharyngeal wall.

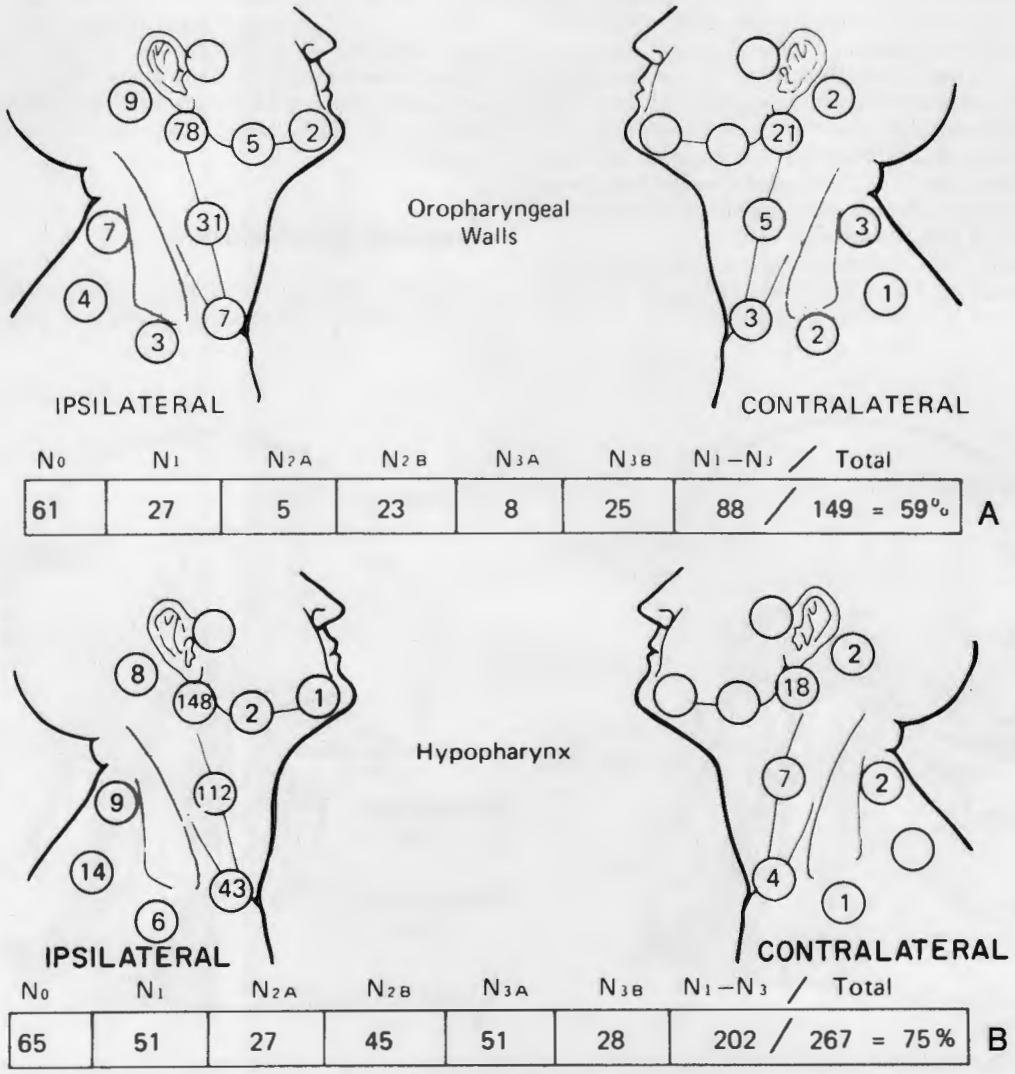
Oropharyngeal Walls
IPSILATERAL
CONTRALATERAL
N0 N1 N2A N2B N3A N3B N1–N3 / Total
61 27 5 23 8 25 88 / 149 = 59%
A
Hypopharynx
IPSILATERAL
CONTRALATERAL
N0 N1 N2A N2B N3A N3B N1–N3 / Total
65 51 27 45 51 28 202 / 267 = 75%
B

Figure 20-1. Nodal distribution on admission, M. D. Anderson Hospital, 1948–1965. (*A*) Oropharyngeal walls. (*B*) Hypopharynx. (Lindberg RD. Distribution of cervical lymph node metastases from squamous cell carcinoma of the upper respiratory and digestive tracts. Cancer 1972;29:1448)

The lymphatics of the pharyngeal walls terminate primarily in the jugular chain with a secondary avenue by way of the spinal accessory chain. The jugulodigastric node is the most commonly involved lymph node.

Lindberg reported 59% clinically positive nodes on admission; 17% were bilateral.[10] Ballantyne reported a 44% incidence of positive retropharyngeal lymph nodes in moderately advanced carcinoma of the pharyngeal walls and pyriform sinus treated by surgery.[2] Ogura and colleagues reported a 66% incidence of subclinical disease for pharyngeal wall carcinomas.[18]

Byers and coworkers reported subclinical disease in one of five T1 or T2 lesions and five of eight T3 or T4 lesions after elective neck dissection.[4] The distribution of positive lymph nodes after elective neck dissection in 13 patients is shown in Figure 20-2*A*.

Hypopharynx

The distribution and N staging on admission before treatment for 267 previously untreated patients with squamous cell carcinoma of the hypopharynx is shown in Figure 20-1*B*.[10] The capillary lymphatics of the hypopharynx, especially the pyriform sinus, are profuse. The distribution of lymph node metastases is mainly to the jugular chain with a secondary pattern to the junctional and spinal accessory lymph nodes. The subdigastric lymph node is the most commonly involved, but midjugular involvement may occur without subdigastric involvement. The risk of retropharyngeal node involvement is unknown, but the risk seems to increase with extensive neck node disease and spread of the primary lesion toward the oropharyngeal wall.

On admission, 75% of patients have clinically positive lymph nodes and at least 15% have bilateral node involvement. There is essentially no difference in the risk of lymph node metastases by T stage (see Table 6-3 in Chap. 6). Ogura and coworkers reported a 62% incidence of subclinical disease; some of the patients received 1500 to 3000 cGy preoperative irradiation.[18] Biller and associates reported the delayed appearance of contralateral nodes in 9% of patients having a pathologically positive ipsilateral neck dissection.[3] The risk for late-appearing contralateral lymph nodes was independent of whether the positive ipsilateral lymph nodes were palpable.

Byers and associates reported subclinical disease in two of three T1 or T2 lesions and 16 of 29 T3 or T4 lesions after elective neck dissection.[4] The distribution of positive lymph nodes after elective neck dissection in 32 patients is shown in Figure 20-2*B*.

CLINICAL PICTURE

The hallmark of pharyngeal wall and pyriform sinus cancers is sore throat. Tumors confined to the lateral pharyngeal wall or pyriform sinus produce a unilateral sore throat, a symptom rather specific for cancer since infectious sore throat is bilateral. The patient with pyriform sinus cancer can point to the painful site with one finger, while the patient with inflammatory sore throat does not. Dysphagia, sensation of foreign body, ear pain, blood-streaked saliva, aspiration, and voice change occur later. Weight loss occurs in patients with advanced lesions. A neck mass may be the only presenting complaint.

Physical Examination

Lesions of the posterior pharyngeal wall may be overlooked even by competent physicians because of failure

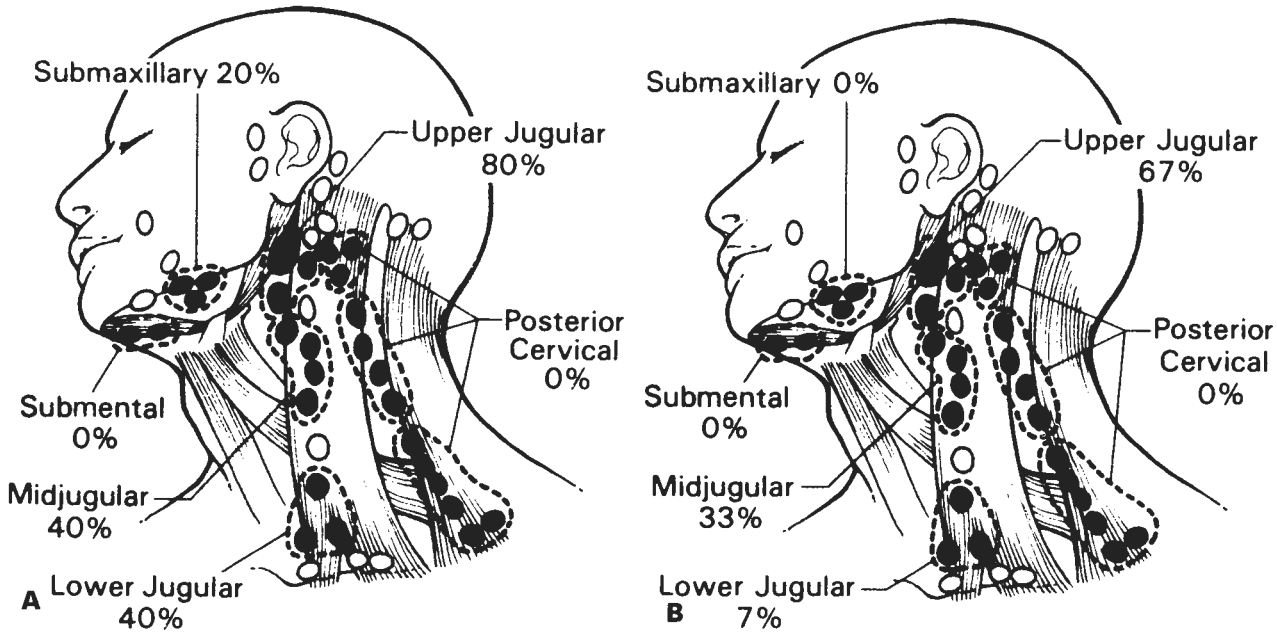

Figure 20-2. The distribution of involved neck nodes after elective modified neck dissection. (*A*) For 13 patients with carcinoma of the pharyngeal wall. (*B*) For 32 patients with carcinoma of the pyriform sinus. (Byers RM, Wolf PF, Ballantyne AJ. Rationale for elective modified neck dissection. Head Neck Surg 1988;10:163–164)

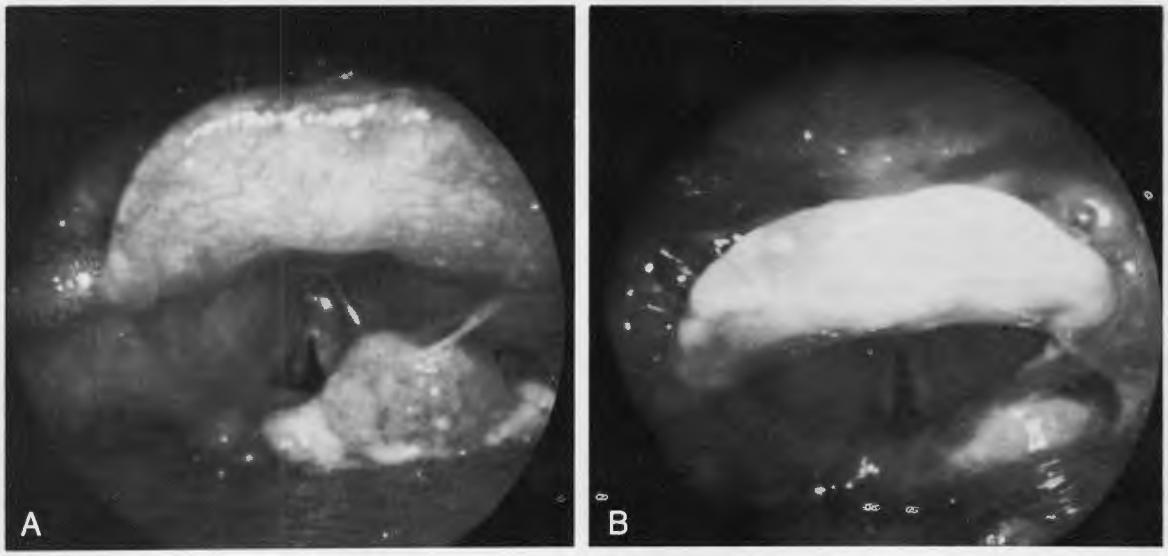

Figure 20-3. (*A*) Exophytic lesion on the left medial wall of the pyriform sinus. It is difficult to determine whether the carcinoma arises from the aryepiglottic fold or the medial wall of the pyriform sinus. (*B*) Photograph after 3000 cGy shows 50% tumor regression. The mass has retracted to the medial wall of the pyriform sinus. The aryepiglottic fold is easily seen.

to look at the posterior pharyngeal wall routinely during indirect laryngoscopy.

Small lesions of the pyriform sinus are easily missed unless careful examinations are done. Many of these patients have active gag reflexes, and complete topical anesthesia coupled with patience is required by the examiner. It may be difficult to differentiate between a lesion arising from the medial wall of the pyriform sinus and one arising from the aryepiglottic fold (Fig. 20-3).

Lesions of the apex of the pyriform sinus or postcricoid area produce indirect findings that are clues to tumor not visible by indirect laryngoscopy. Pooling of secretions in the pyriform sinus and arytenoid area indicates obstruction of the upper gullet. Edema of the arytenoids and inability to see into the apex of the pyriform sinus are clues to postcricoid or low-lying pyriform sinus tumors. Invasion of the palatopharyngeus at its insertion into the inferior constrictor may cause shortening of the muscle and asymmetry of the posterior tonsillar pillars. (Most asymmetry of the posterior tonsillar pillars is due to scarring after tonsillectomy or chronic infection.) As postcricoid tumor enlarges it pushes the larynx anteriorly. This produces a full, expanded neck appearance. The thyroid click, which is produced by the superior thyroid horns hitting against the spine while the thyroid cartilage is rocked back and forth, is lost when the larynx and thyroid cartilage are forced anteriorly by the tumor mass.

METHODS OF DIAGNOSIS AND STAGING

Biopsy Technique

Biopsy of a lesion of the oropharyngeal wall can often be done in the outpatient clinic with the use of topical anesthesia. Biopsy of hypopharyngeal lesions is done under direct visualization and requires general anesthesia.

Staging Procedures

The most important staging tools are indirect and direct laryngoscopy, esophagoscopy, computed tomography (CT) and magnetic resonance imaging (MRI), and chest roentgenography.

Imaging

In the past, the radiographic evaluation of hypopharyngeal tumors included barium swallow, laryngography, xeroradiography, plain film tomography, and soft tissue views of the neck. All of these studies have been replaced by CT and MRI, which should be done before biopsy. Sometimes a tumor of the pyriform sinus will be discovered in a patient during a barium swallow that was ordered to evaluate dysphagia or odynophagia. Barium swallow is never sufficient for staging. Primary methods of diagnosis include direct and indirect laryngoscopy in combination with CT or MRI. CT is preferred at the University of Florida for a variety of reasons discussed in Chapters 4 and 6. MRI is used adjunctively in about 10% of cases for reasons discussed further on in this section.

Examination Techniques

The technical details of CT and MRI are discussed in Chapter 4. These specific techniques applied to the hypopharynx are identical to those used for the larynx (see Chap. 18). Those related to the evaluation of the neck are discussed in Chapter 6.

Imaging of the Normal Anatomy

Normal CT anatomy of the hypopharynx was demonstrated in Figures 18-10 through 18-12 in Chapter 18. The axial anatomy as seen on CT is identical to that on MRI; MRI has better contrast resolution than CT, allowing one

to clearly distinguish the pharyngeal musculature from the mucosa and lymphoid tissue lining the inner wall of the hypopharynx. On MRI, and to a lesser extent CT, the posterior and lateral pharyngeal walls are seen as structures less than 3 mm in thickness. When the thickness approaches the upper limits of this measurement, it is usually because of lymphoid tissue lining the mucosal surfaces or pathologic change; however, lymphoid accumulations tend to be most prominent in the oropharynx, becoming less so as one proceeds inferiorly. (For full discussion of normal variance related to the lymphoid tissue in the upper aerodigestive tract, see the imaging section in Chapter 17.) On T2-weighted MRI, the thin pharyngeal constrictor muscles are relatively easy to distinguish from the higher signal intensity mucosal lymphoid tissue. Enhancement with paramagnetic contrast agents aids in this differentiation on T1-weighted images. When normal, the mucosa is approximately 1 mm thick or less but may appear slightly thicker when the mucosal surfaces of nondistended portions of the airway come to appose one another (Fig. 20-4). (See also Figs. 18-10 through 18-12 in Chap. 18.) The points of penetration of pharyngeal vessels, such as the entrance of the superior laryngeal neurovascular bundle at the upper thyrohyoid membrane, are routinely visible on CT and MRI. These areas are particularly important in patients with cancer since they may provide routes of early perineural and perivascular spread of tumor to the extralaryngeal and extrapharyngeal soft tissues. The fascia of the constrictor muscles is not visible as a separate layer either on CT or on MRI in normal patients; however, inflammation or involvement with erythema may cause the fascia to thicken and become pathologically visible.

The volume of fat lateral and posterior to the pharyngeal wall varies depending on the habitus of individual patients. Normally, a small amount of fat is visible just lateral to the pharyngeal wall in the deep neck in all patients. Little or no fat may be seen in thinner patients between the fascia of the constrictor muscles and that of the prevertebral muscles. Prevertebral muscles are visible in all patients on axial CT and MRI; the prevertebral fascia, however, is not normally visible. The potential retropharyngeal space lies between the fascia of the constrictors and prevertebral fascia.

Above the level of the hyoid, the spaces lateral to the pharynx are referred to as the parapharyngeal space; this anatomy is discussed in detail in Chapters 17 and 23. Below the hyoid bone the carotid sheath structures lie in

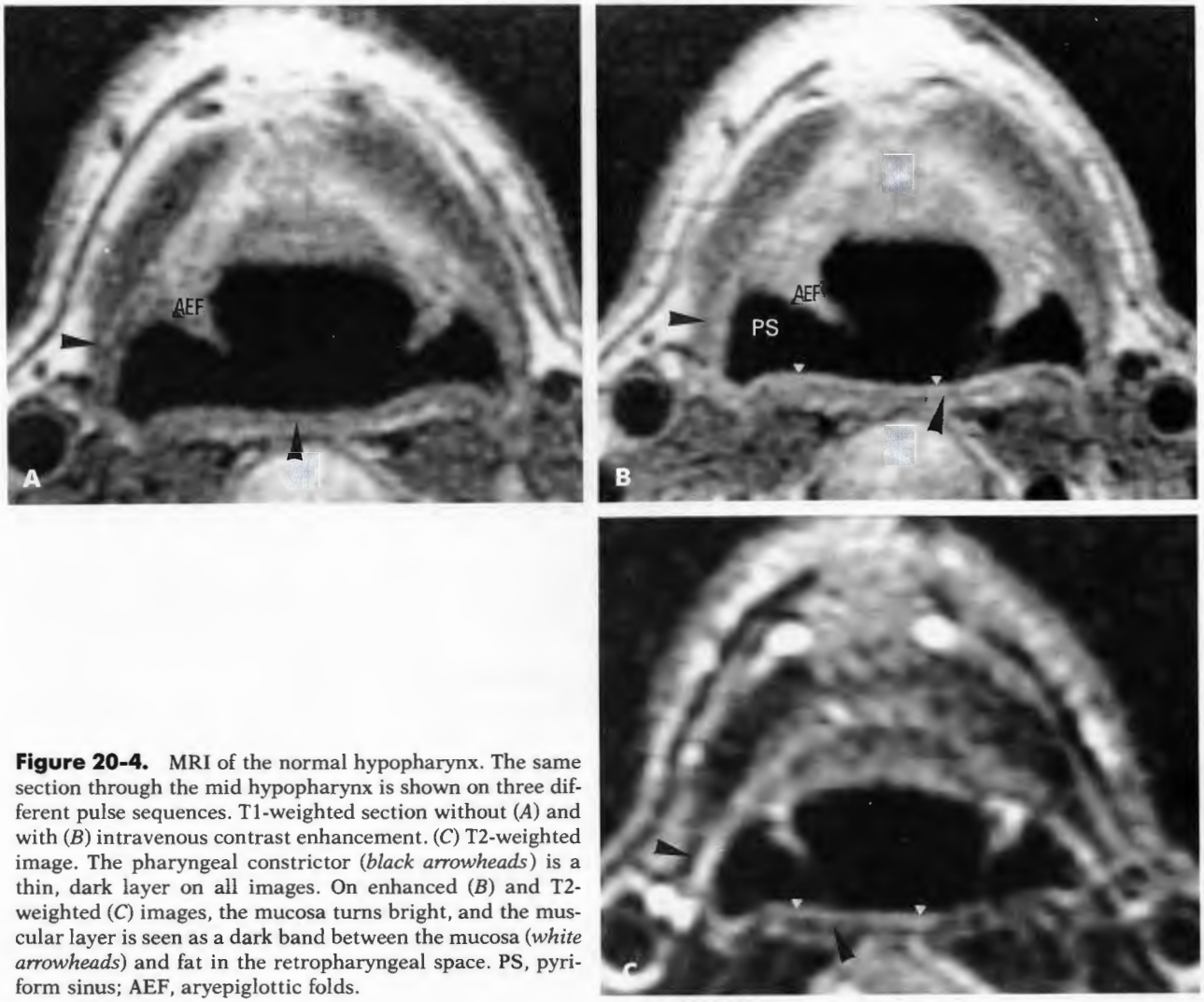

Figure 20-4. MRI of the normal hypopharynx. The same section through the mid hypopharynx is shown on three different pulse sequences. T1-weighted section without (*A*) and with (*B*) intravenous contrast enhancement. (*C*) T2-weighted image. The pharyngeal constrictor (*black arrowheads*) is a thin, dark layer on all images. On enhanced (*B*) and T2-weighted (*C*) images, the mucosa turns bright, and the muscular layer is seen as a dark band between the mucosa (*white arrowheads*) and fat in the retropharyngeal space. PS, pyriform sinus; AEF, aryepiglottic folds.

the fibroadipose envelope of the deep neck which, in turn, surrounds the pharynx laterally. The retropharyngeal lymph nodes lie between the posterolateral corners of the pharynx and the carotid artery from the tip of the clivus to the C3 (hyoid) level.

The deep relationships of the pyriform sinuses, as described in the normal anatomy section of this chapter and illustrated in Figures 18-11 and 18-12 in Chapter 18, are well shown on axial CT and MRI. The degree of distention of the pyriform sinus varies from side to side in any given individual and even more greatly between patients, depending on their anatomy and how the study was done. Since there is usually little lymphoid tissue lining the mucosa of the pyriform sinus, any thickness perceived on the surface usually represents some type of pathology. MRI and CT, however, are not used to evaluate mucosal detail.

Imaging is particularly useful in showing the deep anatomic relationships of the pyriform sinus apex. On contrast-enhanced MRI and CT, the mucosa of the pyriform sinus apex is routinely visible as a thin line that merges medially with the mucosa in the postcricoid region.

The postcricoid portion of the hypopharynx is easily recognized as that zone posterior to the cricoid cartilage, where the pharyngeal constrictor thickens to create the cricopharyngeus muscle. The muscular walls of the postcricoid region are frequently visible on high-resolution CT studies (see Figs. 18-10 through 18-12 in Chap. 18) and somewhat easier to recognize and distinguish from mucosa on T2-weighted or fat-suppressed MRI (see Fig. 21-2*D* in Chap. 21). The lumen is usually not distended with air. Because the pharyngeal lumen is usually collapsed, the mucosa on enhanced CT and MRI is usually seen as parallel lines 1 mm or less in thickness, lying along the inner borders of inferior constrictor (cricopharyngeus) muscle. Normally, the postcricoid region, as seen on axial images, is a somewhat flattened ellipsoid. As the postcricoid region merges with the cervical esophagus (at the esophagus verge), the shape changes to a more round configuration. This transition from postcricoid hypopharynx to esophageal verge occurs at the lower edge of the cricoid cartilage.

Indications for Study

Virtually all hypopharyngeal carcinomas are studied with imaging. CT is used as the primary examination for reasons discussed in Chapters 4 and 6. Both the primary tumor and all cervical and retropharyngeal nodes are studied. Supplemental MRI is most often used to study lesions that on CT are suspicious for submucosal spread toward the esophageal verge.

Imaging is useful in the following specific areas and issues of interest:

- Detecting invasion of the laryngeal framework and extralaryngeal and extrapharyngeal spread to the soft tissues of the neck (Fig. 20-5). This pattern occurs mainly in pyriform sinus primary tumors, although it may be present in those arising on the posterior pharyngeal wall and the postcricoid region. Most pyriform sinus carcinomas are fairly advanced at presentation; however, even ones that appear to be relatively limited will frequently have gross involvement of the laryngeal framework and extralaryngeal spread (Fig. 20-6).[10a]
- Evaluating the inferior extent of the lesion. Imaging can evaluate the pyriform sinus apex and detect submucosal spread in the muscular wall of the postcricoid part of the hypopharynx (see Fig. 20-5). Imaging can also detect continued inferior spread to the esophageal verge and even into the cervical esophagus beneath intact mucosa (Fig. 20-7). Inferior spread beyond the apex into the soft tissues of the neck, tracheoesophageal groove, and thyroid gland can also be detected. These findings can help plan the lower margin of resection and anticipate whether flap reconstruction, gastric pull-up, or some other means of pharyngeal reconstruction will be necessary. It can also help anticipate whether a lower than usual tracheostomy is indicated.
- Demonstrating occult submucosal spread across the midline through the paraglottic and preepiglottic spaces that may obviate partial laryngopharyngectomy (Fig. 20-8)
- Demonstrating early extrapharyngeal spread into the soft tissues of the neck and retropharyngeal space (Fig. 20-9)
- Helping to distinguish between posterior pharyngeal wall carcinoma and tumors of the "party wall"; the latter are classified with primary postcricoid carcinoma (Fig. 20-10). Posterior pharyngeal wall cancers often spare the postcricoid region.
- Detecting spread along the superior laryngeal neurovascular bundle (Fig. 20-11)
- Detecting positive retropharyngeal and neck nodes (see Chap. 6)

Staging

The American Joint Committee on Cancer (AJCC) staging for the hypopharynx is satisfactory for disease of the pyriform sinus but unsatisfactory for the pharyngeal wall[1]:

TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ
T1	Tumor limited to one subsite of hypopharynx
T2	Tumor invades more than one subsite of hypopharynx or an adjacent site, without fixation of hemilarynx
T3	Tumor invades more than one subsite of hypopharynx or an adjacent site, with fixation of hemilarynx
T4	Tumor invades adjacent structures (eg, cartilage or soft tissues of neck)

Lesions of the posterior pharyngeal wall tend to remain on the posterior pharyngeal wall rather than invade the larynx or lateral walls, and therefore fixation and extension to adjacent sites (eg, larynx) do not enter into staging until the lesion becomes advanced. Posterior pharyngeal wall lesions are more appropriately staged by diameter of the tumor, as for lesions of the oropharyngeal wall. A posterior pharyngeal wall lesion could be 6×4 cm with a large central ulceration but confined to the posterior pharyngeal wall and could still be a T1 lesion, when in fact it would have a prognosis similar to a T3 lesion. For this reason, the pharyngeal wall lesions have been staged at the University of Florida using the oropharynx definition of T stage.

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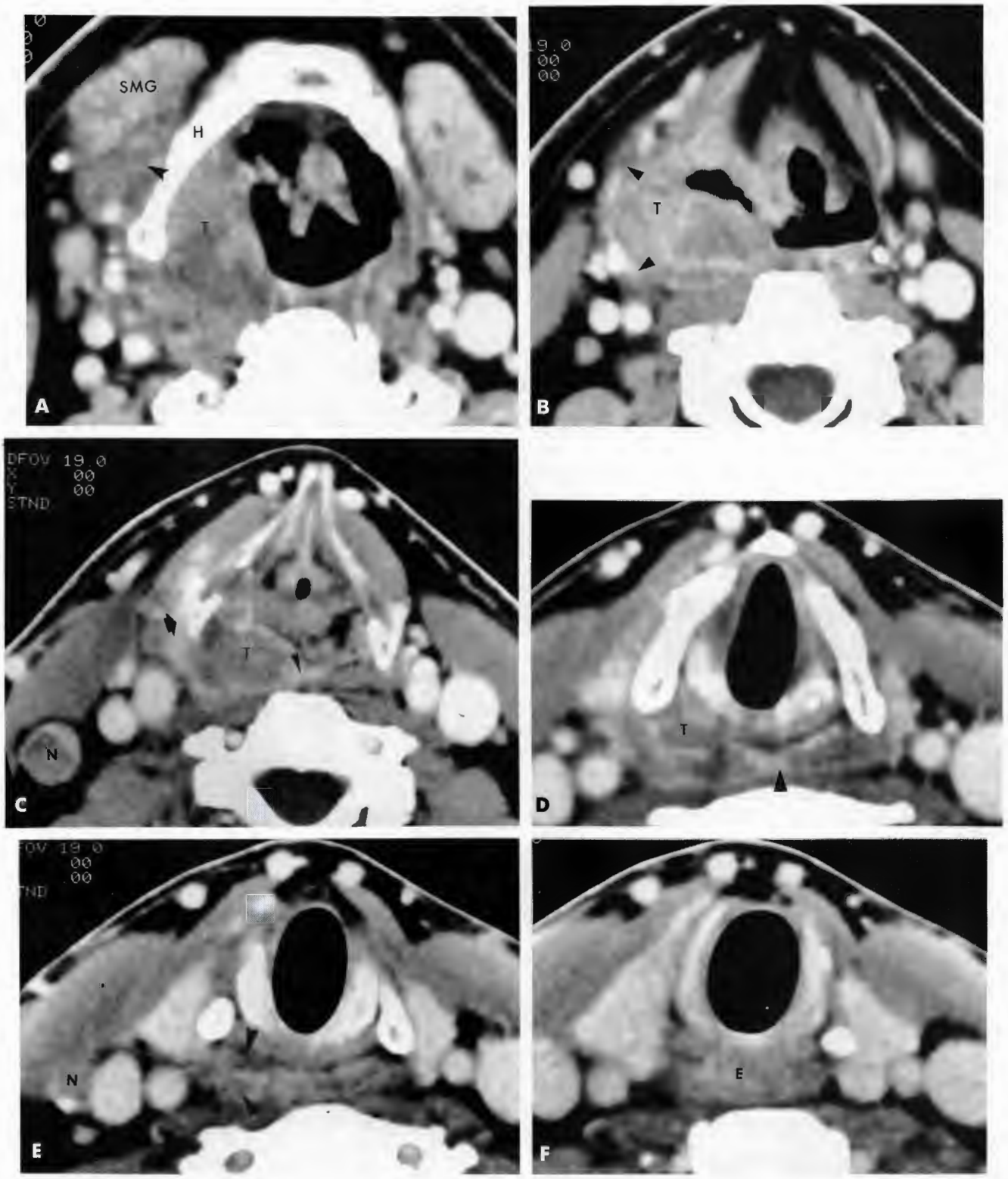


Figure 20-5.

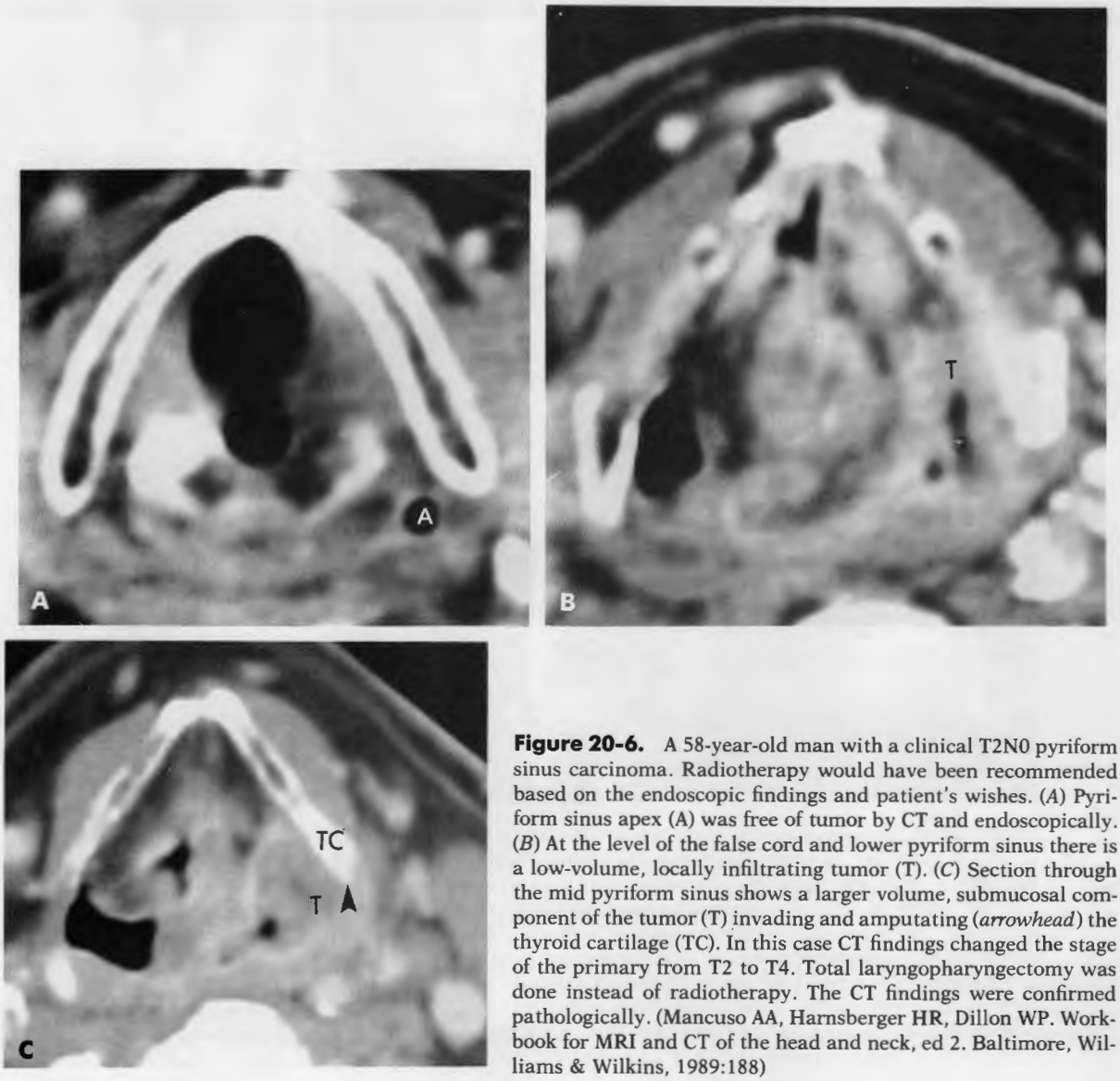


Figure 20-6. A 58-year-old man with a clinical T2N0 pyriform sinus carcinoma. Radiotherapy would have been recommended based on the endoscopic findings and patient's wishes. (*A*) Pyriform sinus apex (A) was free of tumor by CT and endoscopically. (*B*) At the level of the false cord and lower pyriform sinus there is a low-volume, locally infiltrating tumor (T). (*C*) Section through the mid pyriform sinus shows a larger volume, submucosal component of the tumor (T) invading and amputating (*arrowhead*) the thyroid cartilage (TC). In this case CT findings changed the stage of the primary from T2 to T4. Total laryngopharyngectomy was done instead of radiotherapy. The CT findings were confirmed pathologically. (Mancuso AA, Harnsberger HR, Dillon WP. Workbook for MRI and CT of the head and neck, ed 2. Baltimore, Williams & Wilkins, 1989:188)

◄ **Figure 20-5.** A 60-year-old man with a clinical T3N1 pyriform sinus carcinoma. This case demonstrates the typical spread pattern of a moderately advanced lesion. (*A*) Tumor (T) involves the pharyngoepiglottic fold, and extralaryngeal spread (*arrowhead*) is seen between the hyoid bone (H) and submandibular gland (SMG). (*B*) Tumor (T) surrounds the pyriform sinus, unmistakably identifying it as the site of origin. Note the extralaryngeal spread through the thyrohyoid membrane (*arrowheads*). (*C*) Tumor (T) fills the inferior pyriform sinus and spreads across the posterior wall of the pharynx to the midline (*arrowhead*) and to the attachment of the pharyngeal constrictor on the thyroid cartilage (*arrow*). The positive lymph node (N) was palpable. (*D*) Tumor (T) involves the apex of the pyriform sinus and spreads to the midline in the upper postcricoid region (*arrowhead*). Note the normal pharyngeal musculature and intervening fat on the normal side compared with the involved side. (*E*) About 1 cm above the esophageal verge there is subtle but definitive involvement of the pharyngeal wall and surrounding fat (*arrowheads*). Compare the abnormal side with the normal side. A second CT positive node (N) was not palpable. (*F*) No definite evidence of tumor at the esophageal verge (E). In this case, CT findings changed the stage of the primary tumor from T3 to T4 and neck from N1 to N2B. The CT findings helped the surgeons anticipate the need for a myocutaneous flap in the construction of the neopharynx.

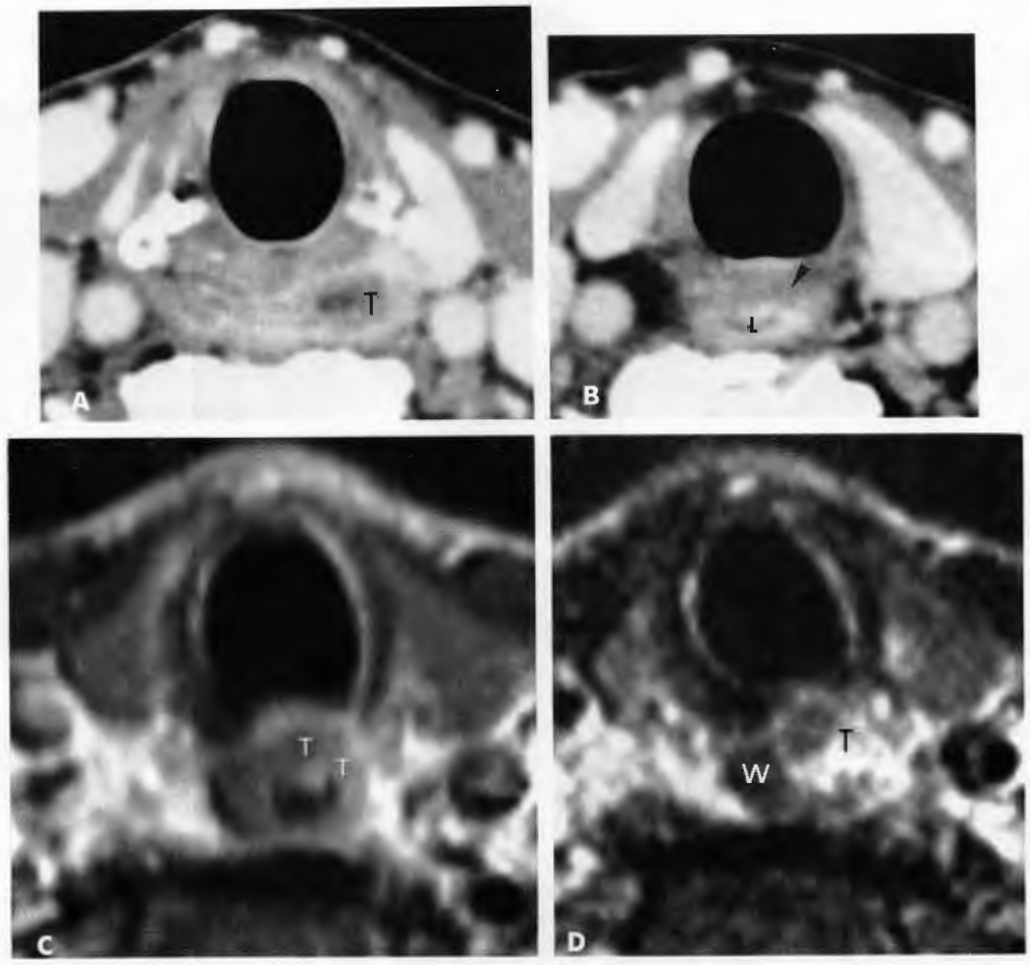


Figure 20-7. A patient with primary carcinoma of the postcricoid region. Endoscopically the tumor appeared to stop at the esophageal verge. The esophageal mucosa was normal. (*A*) CT section 10 to 15 mm above the esophageal verge. A predominantly left-sided infiltrating tumor (T) is present. (*B*) CT section 5 to 10 mm into the cervical esophagus shows very subtle thickening of the anterior and left wall of the esophagus (*arrowhead*), making the lumen (L) appear eccentrically posterior. This is suggestive of an infiltrating mass in the left anterior and lateral esophageal wall. (*C*) Contrast-enhanced MRI at the same level as the CT section in (*B*) shows a thickened, slighty enhancing anterior and left lateral wall of the esophagus (T), strongly suggesting tumor involvement. (*D*) T2-weighted MRI at the same level as (*B* and *C*) showing the tumor (T) infiltrating the left side of the esophagus compared with the more normal esophageal wall (W) on the right.

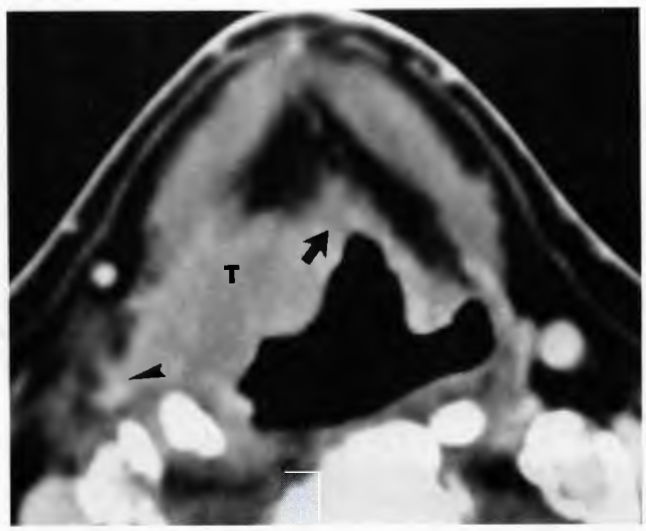


Figure 20-8. A 62-year-old man with pyriform sinus carcinoma clinically staged T3N0. Tumor (T) spreads from the paraglottic space to involve the midline by way of the preepiglottic space (*arrow*). A submucosal bulge was visible endoscopically, but no mucosal disease was present within the laryngeal vestibule. Tumor also spread through the thyrohyoid membrane by way of the superior laryngeal neurovascular bundle (*arrowhead*).

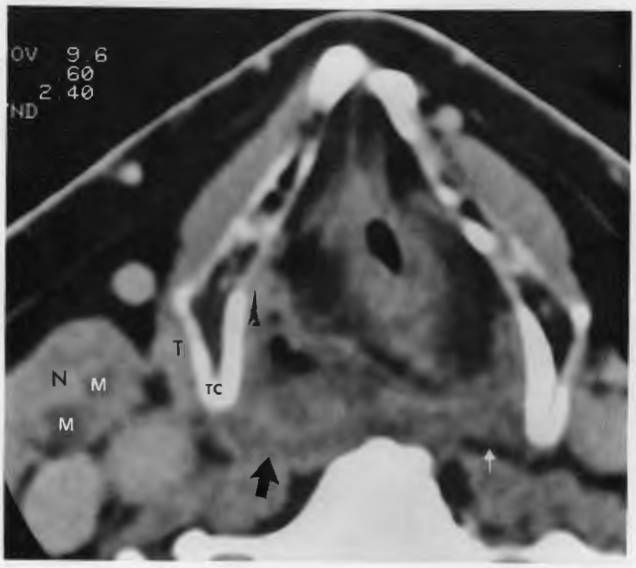


Figure 20-9. A 68-year-old man had a clinical T3N1 hypopharyngeal carcinoma involving the pyriform sinus and posterior pharyngeal wall. There is continued en plaque growth of tumor (T) on the external surface of the thyroid cartilage (TC) at the attachment of the middle pharyngeal constrictor as well as along its inner surface (*arrowhead*). Tumor also obliterates the fat in the retropharyngeal space (*large black arrow*); compare this with the normal side (*white arrow*). Note the metastases (M) in the enlarged neck node (N).

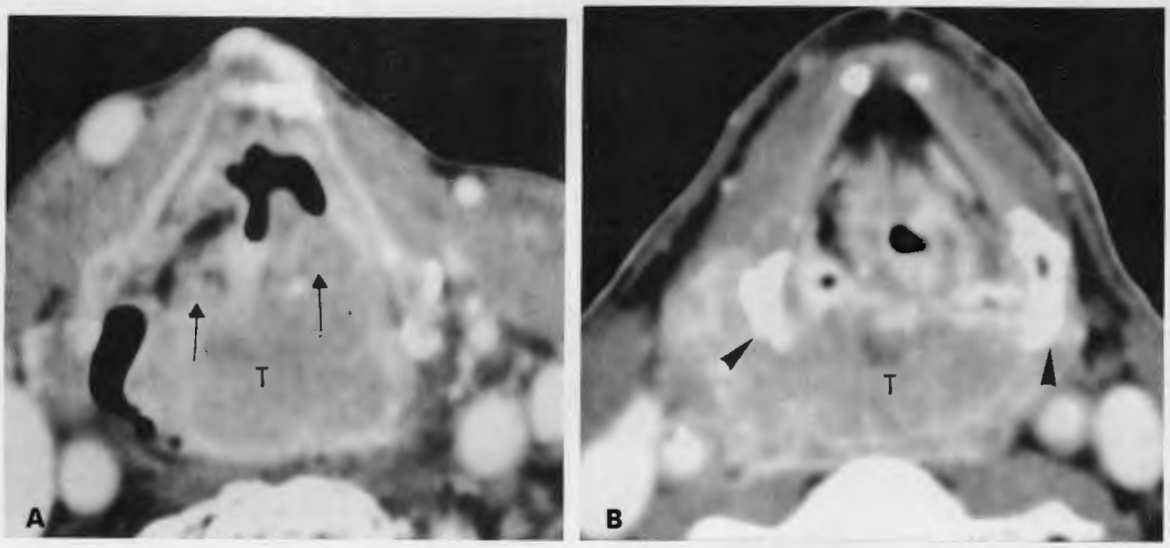


Figure 20-10. Two patients, one with carcinoma of the "party wall" (posterior laryngeal wall, arytenoid pad) and one with with carcinoma of the posterior pharyngeal wall, to contrast the difference in appearance of these lesions. (*A*) Tumor (T) of the posterior *laryngeal* (party) wall is confined to the endolarynx. (*B*) A different patient with a posterior *pharyngeal* wall carcinoma. Note how tumor (T) spreads to the attachment of the pharyngeal constrictor on the posterolateral edges of the thyroid cartilage (*arrowheads*); compare with *A*, where tumor remains within the larynx, conforming to and invading the back surface of the aryepiglottic folds (*arrows*). Both of these tumors continued their growth into the postcricoid region. Posterior pharyngeal wall cancer usually stops its growth at the arytenoid level unless it arises in the postcricoid region (see Chap. 17).

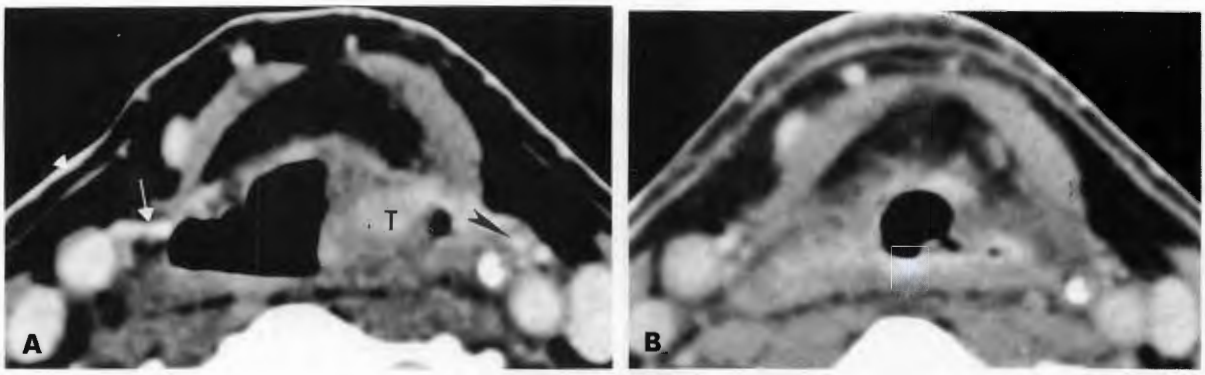


Figure 20-11. (*A*) Pyriform sinus carcinoma spreading out of the pharynx. Clinical stage T2N1 tumor (T) spreading through the thryrohyoid membrane along the superior laryngeal neurovascular bundle (*arrowhead*); compare with normal neurovascular bundle on the opposite side (*white arrow*). (*B*) One year after radiotherapy, a section at the same level as in *A* shows resolution of the spread along the superior laryngeal neurovascular bundle. There is some generalized laryngeal and pharyngeal edema, which is expected following radiotherapy, but no persistent tumor.

TREATMENT

Selection of Treatment Modality

Posterior Pharyngeal Wall

The majority of lesions on the posterior pharyngeal wall are treated by radiation therapy. Attempts have been made to combine surgery and radiation therapy for selected moderately advanced lesions with limited success.

All aspects considered, high-dose radiation therapy will produce cure rates similar to those produced either by surgery alone or through combined surgery plus radiation therapy and with lesser morbidity. Salvage may be achieved by pharyngectomy in a few selected patients whose disease persists or recurs following irradiation.

Lateral Pharyngeal Wall

There is little information specifically related to treatment results for the lateral pharyngeal walls. Small (T1 or T2) lesions are often exophytic and respond readily to irradiation. Larger lesions tend to be deeply infiltrative; local control rates with irradiation are similar to those for the posterior wall. An operation for a large lesion usually implies a laryngectomy in combination with pharyngectomy.

Pyriform Sinus

Lesions confined to the pyriform sinus with normal mobility (T1 or T2) are locally controlled in 80% to 90% of cases by irradiation or partial laryngopharyngectomy.[12,17] Irradiation is our choice at the University of Florida, since it leaves the patient with nearly normal swallowing and speech and provides bilateral coverage of the regional lymphatics including the retropharyngeal lymph nodes. Irradiation is more generally applicable, while there are anatomic and medical restraints to the use of partial laryngopharyngectomy.

Partial laryngopharyngectomy is generally not attempted after 5000 cGy because of increased surgical complications, so if the patient were suitable for partial laryngopharyngectomy at the initiation of radiation treatment, that option might be lost with a trial of radiation therapy.

Lesions that extend outside the pyriform sinus with fixation or reduced mobility of the larynx represent the group of cases where selection of treatment is more complex. These lesions are usually selected for total laryngopharyngectomy plus postoperative radiation therapy, but they may be treated for cure by radiation therapy if apex involvement is minimal and if the primary lesion is mainly confined to the medial wall of the pyriform sinus (Fig. 20-12). A few radiation therapy failures may be salvaged by total laryngopharyngectomy, although the acute surgical morbidity may be considerable after high-dose irradiation.

Some groups have used the response to a trial of chemotherapy to cull out those cases that might have a better chance at cure by irradiation; the results are preliminary at this time. Similarly, a trial of preoperative irradiation to a dose of 4500 to 5000 cGy may be used and the patient reevaluated for full-dose radiation therapy or for surgery depending on the response.

The more advanced, infiltrative lesions are best treated with immediate total laryngopharyngectomy, neck dissection, and postoperative radiation therapy. Preoperative irradiation is advised if the neck nodes are fixed.

Surgical Treatment

Posterior Pharyngeal Wall

If the lesion is located high on the posterior wall, then a transoral approach can be used; for lower lesions the midline mandibulolabial glossotomy approach may be used. Alternatives are the transhyoid or a lateral pharyngotomy approach. The lesion is removed down to the prevertebral fascia, and a skin graft is used to cover the defect; postoperative irradiation is usually recommended.

Figure 20-12. A 54-year-old man presented with poorly differentiated squamous cell carcinoma of the left pyriform sinus. There was a 4×3-cm midjugular node in the right side (*A*) and left side (*B*) of the neck. (*C*) There was an exophytic lesion on the medial wall of the right pyriform sinus extending to the aryepiglottic fold and just onto the laryngeal surface of the epiglottis. The left postcricoid area was invaded submucosally. The right vocal cord was immobile, probably owing to invasion of the cricoarytenoid muscle or joint (T3N3B; stage IV). (*D*) At 3000 cGy, 80% tumor regression was noted. (*E*) Reduced portal at 4600 cGy. The lower border of the original portal was 2 cm below the cricoid; the lower border of the reduced portal is the inferior border of the cricoid cartilage. A strip of midline neck skin is shielded on the reduced portal (*arrow*). (*F*) The final dose to the pyriform sinus and the lymph nodes was 7400 cGy over 6 weeks (120 cGy twice a day). The enlarged lymph nodes disappeared after 4000 cGy, and it was elected to observe the neck. The vocal cord regained full mobility 2 months after treatment. The patient had a normal voice and swallowing at 4 years. (For color photographs see Color Fig. 8*A* and *B* in Chap. 3.)

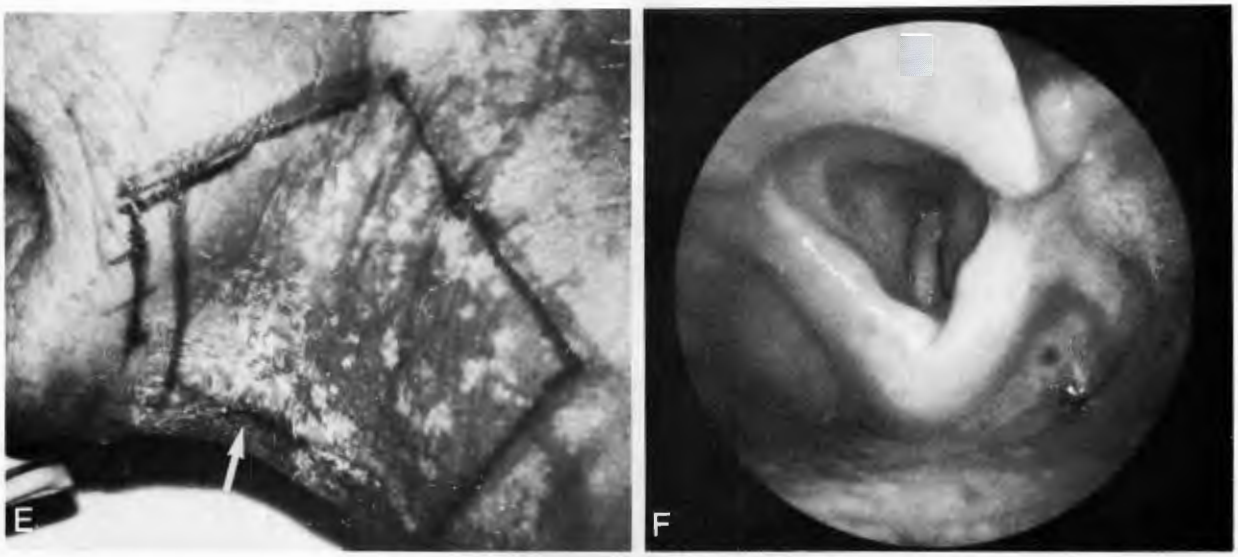


Figure 20-12. (*Continued*)

Pyriform Sinus

PARTIAL LARYNGOPHARYNGECTOMY. A partial laryngopharyngectomy removes the false cords, epiglottis, and pyriform sinus; one arytenoid may be removed when necessary. The vocal cords are preserved.

Partial laryngopharyngectomy can be successfully used for early lesions confined to the pyriform sinus (T1) and selected lesions with minimal extension beyond the pyriform sinus (T2). In our clinic its use is advised only when radiation therapy cannot be used. The operation could be considered for salvage of a radiation therapy failure or for poor response to an initial trial of radiation therapy; these latter two situations occur infrequently and require surgical expertise. The following findings contraindicate partial laryngopharyngectomy:

- Extension to apex of the pyriform sinus
- Fixed cord
- Extension to contralateral arytenoid
- Poor pulmonary function
- Large, fixed lymph nodes

The apex of the pyriform sinus lies opposite the cricoid cartilage, and since the cricoid is the only cartilage that forms a complete ring about the airway, it must remain intact to prevent collapse. There is a greater tendency to aspiration after partial laryngopharyngectomy compared with supraglottic laryngectomy, and the patient must have the motivation to relearn to swallow.

TOTAL LARYNGOPHARYNGECTOMY. Laryngopharyngectomy removes the larynx and varying amounts of pharyngeal wall. Advanced lesions require excision of nearly the entire circumference. The pharynx is reestablished by primary closure after a partial pharyngectomy, but a flap is required after total pharyngectomy. Since almost all these patients receive postoperative radiation therapy, the operation should be planned for one-stage reconstruction to avoid delays. A planned controlled fistula speeds the healing process and largely eliminates the occurrence of an uncontrolled fistula, which delays healing and the start of radiation therapy. If a myocutaneous flap is used, a controlled fistula is unnecessary.

Postcricoid

Postcricoid carcinoma generally requires a total laryngopharyngectomy with immediate reconstruction, generally using a pectoralis major myocutaneous flap. If the lesion extends into the cervical esophagus, then reconstruction becomes more difficult (see Chap. 21).

Irradiation Technique

Posterior Pharyngeal Wall

The irradiation technique for lesions of the posterior pharyngeal wall is opposed lateral fields to include the primary lesion and the regional nodes (Fig. 20-13).[15,18a] Since these lesions tend to have mucosal skip areas, the entire posterior pharyngeal wall is included initially. If the lesion extends near the level of the arytenoids, the postcricoid pharynx, pyriform sinus, and upper cervical esophagus are included. The jugular chain, spinal accessory, and retropharyngeal lymph nodes are included even if the neck nodes are negative. The anterior border does not flash and spares the anterior one third of the glottis.

High-energy x-rays (17 to 22 MV) are preferred for the initial portion of the treatment if the neck nodes are negative, since this places the 90% to 95% depth dose at the tumor, with sufficient dose to the lymph nodes for subclinical disease. If the nodes are positive, then cobalt-60 (^{60}Co) or 4- to 6-MV irradiation is used for the initial portion of the treatment on the side with involved nodes.

The critical portion of the treatment occurs when the portals are reduced at 4500 cGy to avoid the spinal cord. The primary lesion frequently extends behind the plane of the anterior borders of the cervical vertebra (see Fig. 20-13*C*). The posterior border of the portal (see Fig. 20-13*B*) is placed at the posterior edge of the cervical vertebral bodies. The central axis is set at the posterior border of the portal to avoid beam divergence. Wedges improve the distribution. The beam energy is ^{60}Co or 4 to 8 MV; 17 MV gives a poorer distribution for the reduced portal (see Fig. 20-13*D*). Daily portal and imaging films and precision setups are required. As much of the larynx as possible is shielded.

A gastrostomy tube has been placed before irradiation in a few patients to ensure nutrition; this is better tolerated than a small nasogastric tube. There is little likelihood of surgical salvage after radiation therapy failure, so every effort should be made to assist the patient through the acute effects to gain a reasonable chance of cure.

A time–dose analysis for local control shows a dependence on fraction size and total dose for T2 and T3 lesions (see Chap. 12). A dose of 200 cGy per fraction is recommended for one-fraction-a-day schemes. The total dose is 6000 to 6600 cGy for T1 and 6600 to 7000 cGy for T2 and T3; the dose per fraction may be increased to 215 to 225 cGy to the final reduced portals to shorten the overall time.

Twice-daily fractionation plus the aforementioned improvements in technique for the reduced fields has produced improved control rates. A dose of 120 cGy twice daily with a 6-hour interval is used. The dose for T2 and T3 lesions is 7440 to 7680 cGy; higher doses are not recommended unless laryngeal structures can be excluded from the portals.

External-beam irradiation may be supplemented by single-plane implants (Fig. 20-14). Our results with ex-

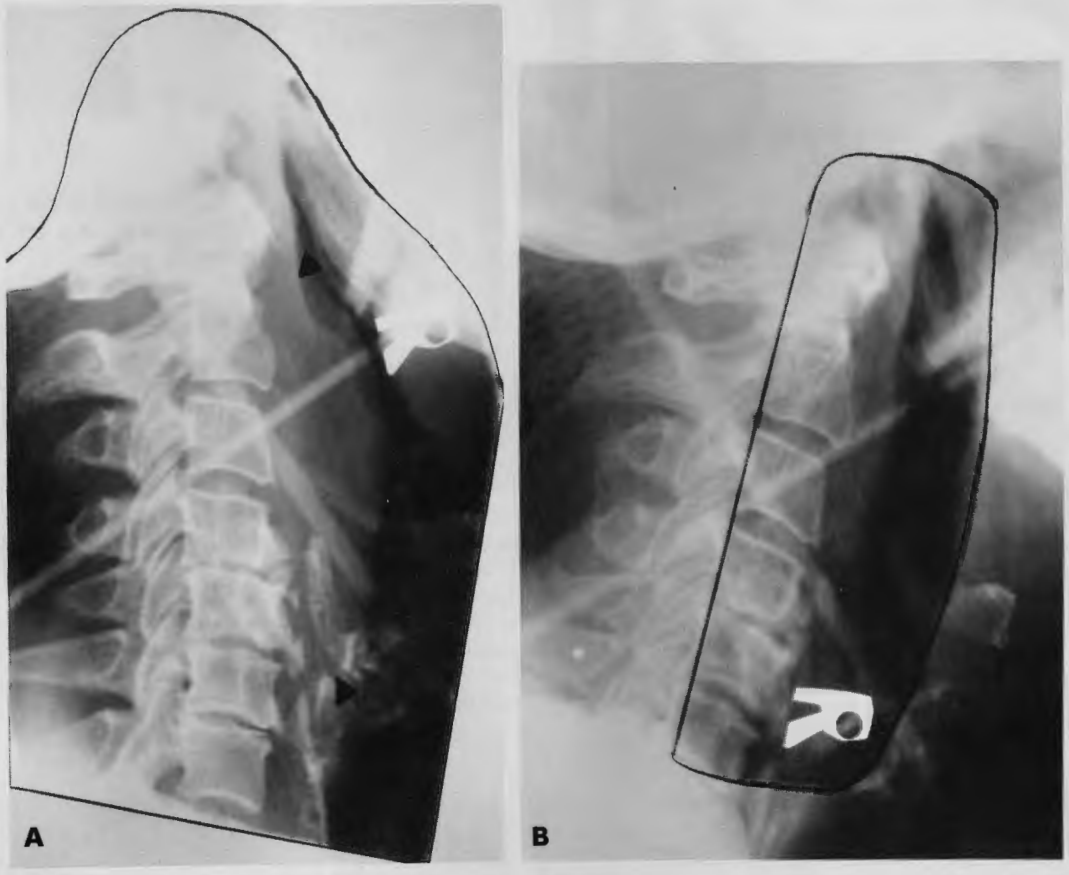
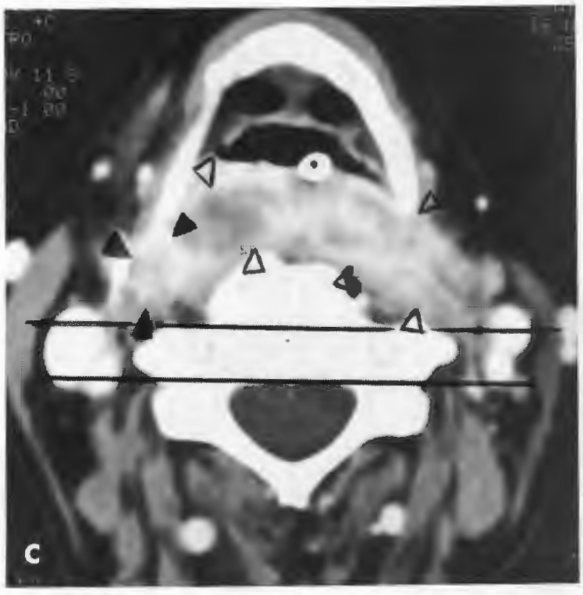


Figure 20-13. (*A*) Initial treatment fields for a T3N2B squamous cell carcinoma of the posterior pharyngeal wall. Arrowheads indicate the superior and inferior margins of the tumor. The anterior border does not flash the skin of the neck. The anterior third of the glottis can usually be shielded. (*B*) Treatment fields after reducing off the spinal cord. Note that the posterior edge of the field is at the posterior aspect of the vertebral bodies. Daily imaging films are requested to check the accuracy of alignment. (*C*) Computed tomogram prior to treatment. The open arrowheads denote the primary tumor, and the closed arrowheads indicate a retropharyngeal node. Note that there is tumor extending posterior to the anterior surface of the vertebral body. If the field edge bisects the vertebral body when the spinal cord is shielded, part of the cancer will be in the penumbra or altogether outside the treatment volume. The posterior line indicates the field margin if it is placed at the posterior edge of the vertebral bodies. There is no beam divergence as the central axis is placed at the posterior edge of the field. (*D*) Isodose plots for reduced portals. In our practice, 6 MV or 8 MV x-rays are the ideal energy. Because of the characteristics of high-energy (eg, 17 MV) x-rays near field edge, isodose distributions are constricted compared with 8 MV. The result is reduced dosage to cancer near the posterior field edge, which is undesirable in treatment of posterior pharyngeal wall cancer. The central axis is placed at the posterior field edge to provide a nondivergent posterior field edge. Wedges are used to reduce the dose anteriorly and to pull the isodose distribution slightly posteriorly. SSD, source to surface distance; CA, central axis. (*A* through *C* from Mendenhall WM, Parsons JT, Mancuso AA, Cassisi NJ, Million RR. Squamous cell carcinoma of the pharyngeal wall treated with irradiation. Radiother Oncol 1988;11:210–211; *D* from Parsons JT, Mendenhall WM, Bova FJ, Million RR. Head and neck cancer. In: Levitt SH, Khan FM, Potish RA (eds). Levitt and Tapley's Technological basis of radiation therapy: practical clinical applications, ed 2. Philadelphia, Lea & Febiger, 1992:207)



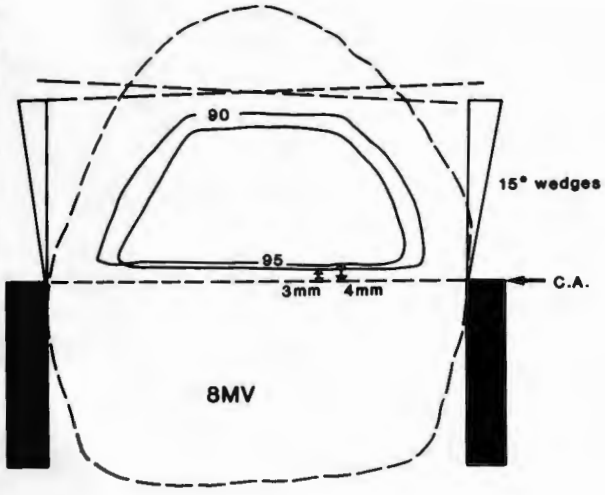


Figure 20-13. (*Continued*)

ternal-beam have improved, and we have discontinued the implants.

Pyriform Sinus

RADICAL IRRADIATION. The superior aspect of the pyriform sinus lies at the pharyngoepiglottic fold which corresponds to the level of the hyoid bone. The inferior border (apex) corresponds to the inferior border of the cricoid.

Parallel opposed lateral portals are used to encompass the primary lesion and regional nodes on both sides (Figs. 20-15 through 20-17).[13,18a] The superior border is placed 2 to 3 cm above the tip of the mastoid to cover junctional lymph nodes. The retropharyngeal lymph nodes lie at the anterior edge of C1 and C2 and must be included. The posterior border encompasses the spinal accessory lymph nodes. The spinal cord is shielded after 4500 cGy. Clinically positive nodes behind the plane of the spinal cord require the addition of a neck dissection or electron boosts. The anterior border is usually placed about 1 cm behind the anterior skin edge. When the anterior skin is shielded, the radiation therapist checks the setup daily because the margin for error is slim. Protec-

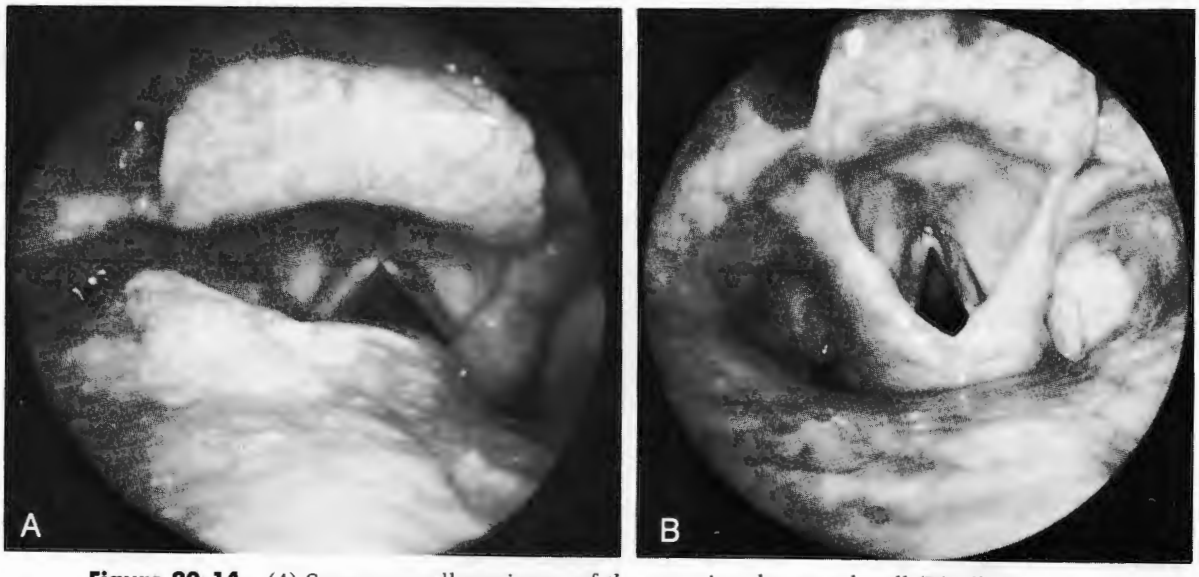


Figure 20-14. (*A*) Squamous cell carcinoma of the posterior pharyngeal wall (T2N0). Treatment plan was external-beam irradiation, 6000 cGy over 6 weeks, and gold grain implant 2000 to 2500 cGy. (*B*) No evidence of disease at 3 years. (For color photographs see Color Figure 8*C* and *D* in Chapter 3.)

tion of the strip of anterior skin and subcutaneous tissue is thought to be important in providing an escape route for lymph through the dermal lymphatics, thereby reducing lymphedema of the larynx. Clothespins are sometimes used to isolate the tissues from the beam (Fig. 20-18). The inferior border is placed at least 1 to 2 cm below the inferior border of the cricoid for early lesions and lower for lesions with inferior extension.

There is usually a small area of unirradiated lower neck lymph nodes remaining when the inferior border is 2 cm below the cricoid. A small anterior low neck field is added to cover the lower jugular nodes, even for patients with a clinically negative neck. The tendency for pyriform sinus cancer to produce multiple nodes and frequent involvement of the inferior jugular and occasionally the paratracheal nodes indicates generous coverage for elective neck irradiation.

The beam is ^{60}Co or 4 to 6 MV. Dosimetry is individualized using wedges, compensators, and unequal loadings as needed. Dose recommendations are given in Table 20-1. (For dose analysis, see Chap. 12.) Because twice-a-day fractionation schemes have given excellent results in several instances (see Figs. 20-15 and 20-19), this is the preferred treatment scheme.

POSTOPERATIVE IRRADIATION. Opposed lateral portals are used for the upper neck portals and extend superiorly to include the junctional and lateral retropharyngeal lymph nodes, the base of the tongue, and the pharyngeal walls. With negative margins and fewer than four indications for postoperative irradiation, the dose is 6000 cGy over 6 to 7 weeks with reduction off the spinal cord at 4500 cGy. The dose is increased to 6500 to 7000 cGy for positive margins or more than three indications for therapy.

The lower neck is treated by an en face portal that includes the stoma. The usual dose is 5000 cGy given dose, but it may be higher in selected situations. The dose to the stoma is frequently boosted to 6000 cGy. (See Chap. 6 for further details on postoperative radiation therapy.)

Portals for preoperative irradiation are similar to those described in the section on radical irradiation.

Combined Treatment Policies

Posterior Pharyngeal Wall

If the pharynx is to be reconstructed by a gastric "pull-up," we prefer to use preoperative irradiation so that it will not be necessary to irradiate the stomach.

TABLE 20-1. Carcinoma of the Pyriform Sinus: Dose Guidelines

Stage	One Fraction per Day	Two Fractions per Day (120 cGy per Fraction)
T1–T2	6000 cGy over 6 weeks 6500 cGy over 7 weeks	7440 cGy
T2–T3	6400 cGy over 6½ weeks 7000 cGy over 8 weeks	7440–7680 cGy

(See Chap. 21.) The usual dose is 5000 cGy. If the defect is to be reconstructed with an ileal free graft, postoperative irradiation is preferred to avoid damage to the small blood vessels used for the anastomoses. A dose of 6000 cGy is used with negative margins and increased to 6500 to 7000 cGy for positive margins or greater than four indications for irradiation. Treatment planning is described under postoperative irradiation.

Pyriform Sinus

Irradiation may be recommended before operation for patients with a large fixed node to reduce the size of the mass and to help obtain surgical margins. The preoperative dose is usually limited to 4500 to 5000 cGy to the primary lesion, but the dose to the large lymph nodes may be 6000 cGy or more depending on the response. (See Fig. 6-38 in Chap. 6.)

After total laryngopharyngectomy with or without radical neck dissection, radiation therapy is recommended if there are close or positive margins, multiple or large positive nodes, extension of nodal disease through the capsule, or cartilage invasion. There is an increased risk of pharyngeal stenosis, especially if the pharyngeal closure is tight. El-Badawi and coworkers showed a significant reduction in failure above the clavicle and an increased survival rate when comparing surgery alone to surgery plus postoperative radiation therapy.[7]

Management of Recurrence

Posterior Pharyngeal Wall

Recurrence after radiation therapy may be limited to the posterior pharyngeal wall and may be suitable for surgical excision with occasional salvage. Meoz-Mendez and associates reported 11 of 68 local failures salvaged.[16] There has been no permanent salvage in 26 radiation therapy failures at the University of Florida. Irradiation salvage after surgical failure would be unusual.

Pyriform Sinus

The hallmark of local recurrence after radical irradiation is persistent major edema, inability to visualize the pyriform sinus, ear pain, pain on swallowing, and fixation of laryngeal structures. Direct laryngoscopy and biopsy are required, but biopsy results may be negative and misleading. Eventually a decision may be made to recommend total laryngopharyngectomy for salvage without positive biopsy findings.

Irradiation failures may occasionally be salvaged by total laryngopharyngectomy and neck dissection. The risk of major morbidity such as fistula formation is high.

Recurrences after total laryngopharyngectomy usually occur in the soft tissues of the neck, the untreated opposite neck, the base of the tongue, or the stoma. Some patients may be salvaged by radiation therapy.[19] After failure of partial laryngopharyngectomy, patients may be rescued by total laryngopharyngectomy.

(text continues on page 524)

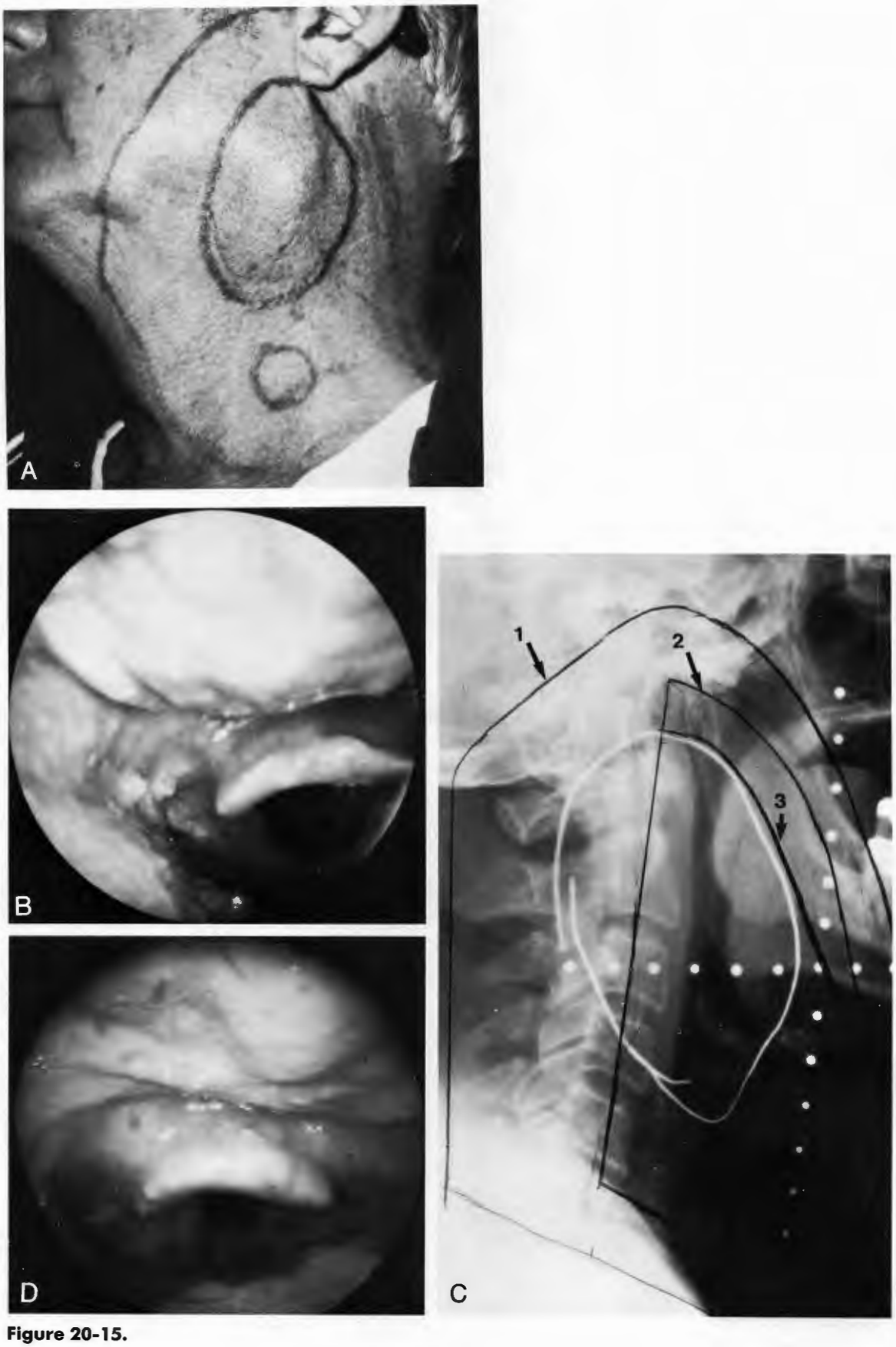


Figure 20-15.

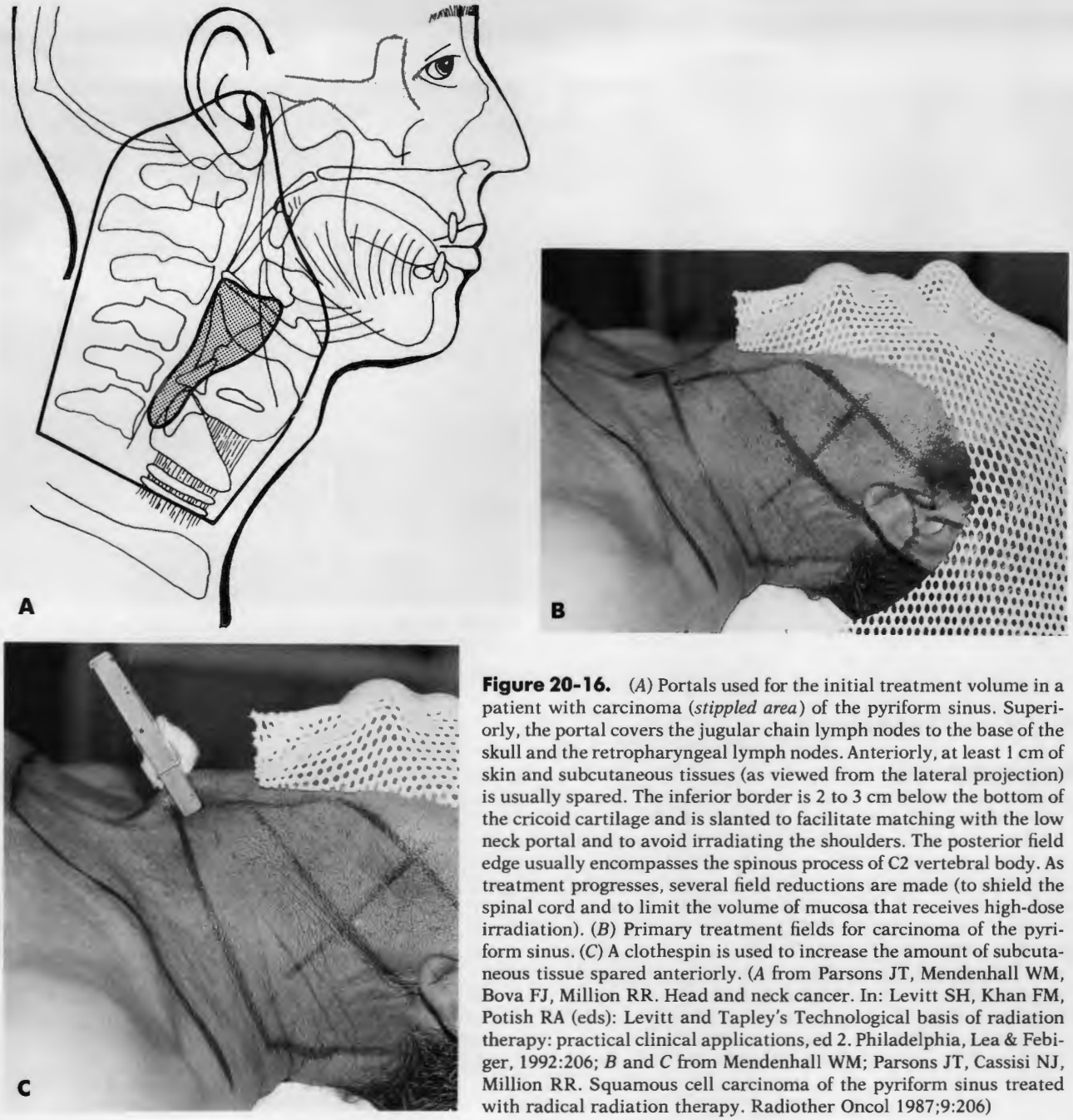


Figure 20-16. (*A*) Portals used for the initial treatment volume in a patient with carcinoma (*stippled area*) of the pyriform sinus. Superiorly, the portal covers the jugular chain lymph nodes to the base of the skull and the retropharyngeal lymph nodes. Anteriorly, at least 1 cm of skin and subcutaneous tissues (as viewed from the lateral projection) is usually spared. The inferior border is 2 to 3 cm below the bottom of the cricoid cartilage and is slanted to facilitate matching with the low neck portal and to avoid irradiating the shoulders. The posterior field edge usually encompasses the spinous process of C2 vertebral body. As treatment progresses, several field reductions are made (to shield the spinal cord and to limit the volume of mucosa that receives high-dose irradiation). (*B*) Primary treatment fields for carcinoma of the pyriform sinus. (*C*) A clothespin is used to increase the amount of subcutaneous tissue spared anteriorly. (*A* from Parsons JT, Mendenhall WM, Bova FJ, Million RR. Head and neck cancer. In: Levitt SH, Khan FM, Potish RA (eds): Levitt and Tapley's Technological basis of radiation therapy: practical clinical applications, ed 2. Philadelphia, Lea & Febiger, 1992:206; *B* and *C* from Mendenhall WM; Parsons JT, Cassisi NJ, Million RR. Squamous cell carcinoma of the pyriform sinus treated with radical radiation therapy. Radiother Oncol 1987;9:206)

◄ **Figure 20-15.** A 64-year-old man had a history of mild sore throat for 1 year. One month prior to admission he felt a small, 1-inch knot in his neck. A biopsy of the neck showed squamous cell carcinoma; the mass enlarged rapidly after biopsy. (*A*) There was a 6×4-cm fixed mass in the upper neck with a well-healed biopsy scar. There was a 3×2-cm mobile low jugular lymph node. The lymph nodes are circled and the left lateral portal is outlined. The lower neck was irradiated through an anterior portal. (*B*) There was a small nodular lesion of the anterior wall of the left pyriform sinus with minimal extension to the medial and lateral wall. The apex was free of disease. There was early extension to the pharyngoepiglottic fold and vallecula. Mobility was normal (T2N3A). (*C*) Simulation film. The wire indicates the limits of the large lymph node. The initial treatment volume (1) received 4560 cGy; the first reduced portal (2) was carried to 6000 cGy and the final reduced portal (3) to 7680 cGy (120 cGy twice a day) over 6½ weeks. The dose to the posterior strips was boosted to 6500 cGy with 10-MeV electrons. The right lower neck recieved 5000 cGy given dose and the left lower neck mass received 6000 cGy given dose in 6 weeks. The large neck mass was reduced to 2 cm by the time of left neck dissection. Pathologic examination revealed pleomorphic squamous cell carcinoma in 2 of 16 lymph nodes. (*D*) Photograph at 18 months show mild (1+) edema of the epiglottis and aryepiglottic folds. The edema disappeared by 2 years. The patient was living, free of disease, at 11 years with mild dysphagia.

Figure 20-17. Carcinoma of the pyriform sinus: En face low neck field with midline trach block. (Mendenhall WM, Parsons JT, Cassisi NJ, Million RR. Squamous cell carcinoma of the pyriform sinus treated with radical radiation therapy. Radiother Oncol 1987;9:206)

Figure 20-18. Clothespins applied to anterior midline strip of skin and subcutaneous tissues to increase the amount of tissue shielded. The portal is aligned with skin marks before the clamps are applied.

RESULTS OF TREATMENT

Pharyngeal Wall

The treatment policy at the University of Florida has been primarily to use radical irradiation. The local control rate for 74 patients (75 lesions) treated by continuous-course irradiation (62 lesions were mostly in the hypopharynx and 57 were located on the posterior pharyngeal wall) is shown in Table 20-2.[15] The local control rate during the 1964 to 1978 era was poor. The local control rates (1978 to 1989) have improved considerably with a modification in technique plus use of the twice-a-day fractionation plan; Parsons reported local control rates of 2 of 2 for T1 lesions, 8 of 10 for T2 lesions (greater than 2 to 4 cm), and 8 of 12 (67%) for T3 lesions (greater than 4 to 6 cm) (Parsons JT, personal communication, March 1991).

Meoz-Mendez and coworkers reported the results of radiation therapy alone for 164 patients with lesions arising from the posterior and lateral pharyngeal walls.[16] The local control by T stage and the salvage after radiation therapy failure are shown in Table 20-3. The cause of death was local failure in 38%, neck recurrence in 6%, distant metastases in 10%, and second primary cancer in 16%.

Marks and coworkers compared low-dose preoperative radiation therapy (2500 to 3000 cGy) followed by operation to radiation therapy alone (Table 20-4).[11] The local control rate was better for the combined group, but

TABLE 20-2. Pharyngeal Wall Carcinoma: Local Control (No. Controlled/No. Treated—75 Tumors in 74 Patients)

T Stage*	Excluded†	Once-a-day Frationation External Beam	Once-a-day Fractionation External Beam + Interstitial Implant	Twice-a-day Fractionation‡ External Beam	Total Local Control	No. Salvaged/ No. Attempted	Ultimate Local Control
T1	1	2/3	No data	1/1	3/4	0/1	3/4
T2	3	7/12	1/5	4/4	12/21 (57%)	1/3	13/21 (62%)
T3	7	8/19	0/2	4/6	12/27 (44%)	1/2	13/27 (48%)
T4	2	1/6	0/2	1/2	2/10 (20%)	0/0	2/10 (20%)

* Oropharyngeal T stage using the AJCC system.

† Patients were excluded from the analysis of disease control at the primary site and/or neck if they died less than 2 years from treatment with that site(s) continuously disease-free.

‡ See text for local control rates as of March 1991.

(Mendenhall WM, Parsons JT, Mancuso AA, Cassisi NJ, Million RR. Squamous cell carcinoma of the pharyngeal wall treated with irradiation. Radiother Oncol 1988;11:207)

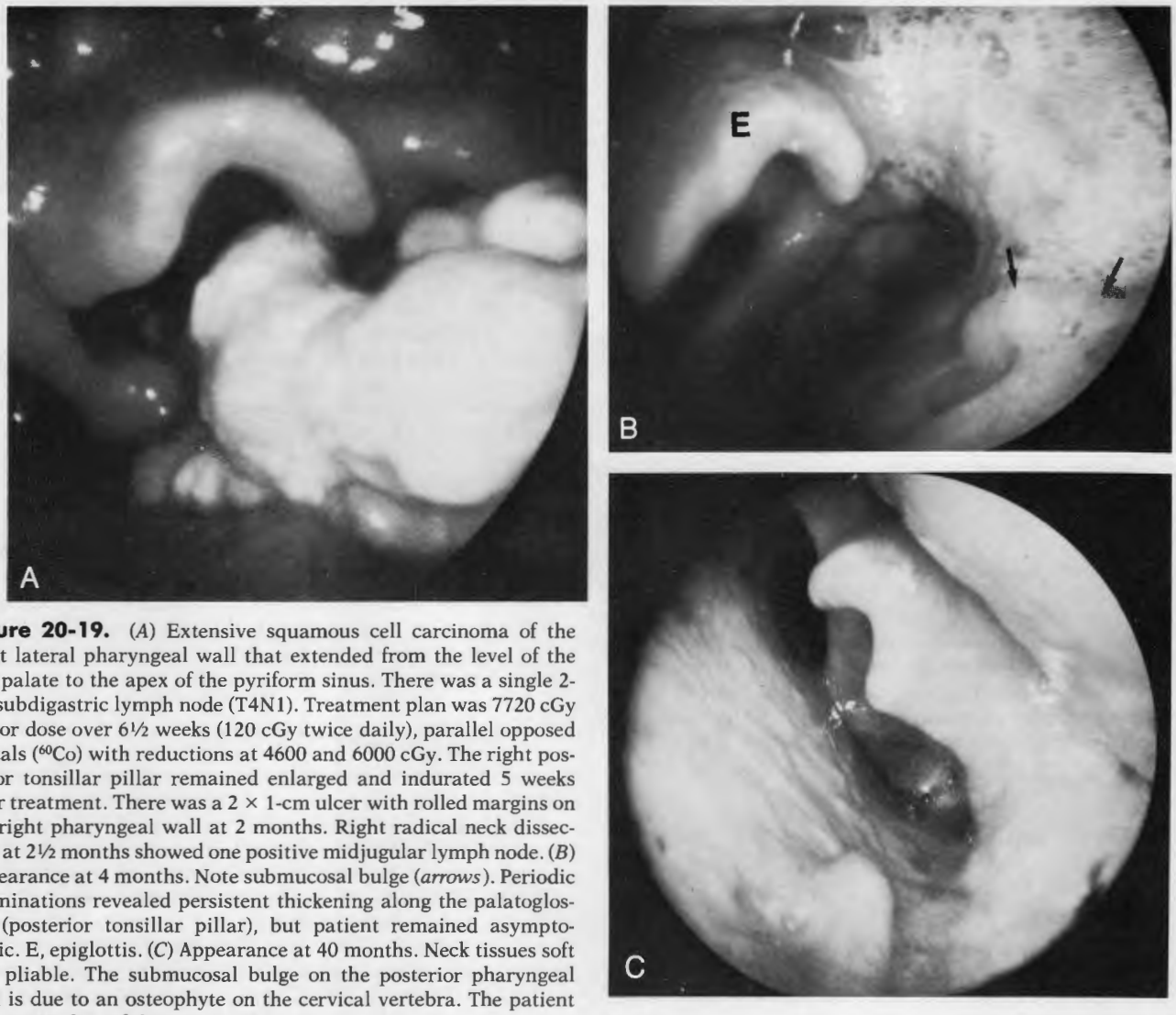


Figure 20-19. (*A*) Extensive squamous cell carcinoma of the right lateral pharyngeal wall that extended from the level of the soft palate to the apex of the pyriform sinus. There was a single 2-cm subdigastric lymph node (T4N1). Treatment plan was 7720 cGy tumor dose over 6½ weeks (120 cGy twice daily), parallel opposed portals (^{60}Co) with reductions at 4600 and 6000 cGy. The right posterior tonsillar pillar remained enlarged and indurated 5 weeks after treatment. There was a 2 × 1-cm ulcer with rolled margins on the right pharyngeal wall at 2 months. Right radical neck dissection at 2½ months showed one positive midjugular lymph node. (*B*) Appearance at 4 months. Note submucosal bulge (*arrows*). Periodic examinations revealed persistent thickening along the palatoglossus (posterior tonsillar pillar), but patient remained asymptomatic. E, epiglottis. (*C*) Appearance at 40 months. Neck tissues soft and pliable. The submucosal bulge on the posterior pharyngeal wall is due to an osteophyte on the cervical vertebra. The patient was living, free of disease, at 10 years.

TABLE 20-3. Squamous Cell Carcinoma of the Pharyngeal Walls: Local Control

Stage	Local Control With Radiation Therapy Alone	Surgical Salvage	Ultimate Local Control
T1 (0–2 cm)	10/11 (91%)	1	11/11 (100%)
T2 (2–4 cm)	33/45 (73%)	2	35/45 (78%)
T3 (<4 cm)	38/62 (61%)	6	44/62 (71%)
T4 (massive)	17/46 (37%)	2	19/46 (41%)

Note: M. D. Anderson Hospital; 164 patients treated 1954–1974.
(Adapted with permission from Meoz-Mendez RT, Fletcher GH, Guillamondegui OM, Peters LJ. Analysis of the results of irradiation in the treatment of squamous cell carcinomas of the pharyngeal walls. Int J Radiat Oncol Biol Phys 1978;4:581. Copyright © 1978, Pergamon Press, Ltd)

TABLE 20-4. Carcinoma of the Pharyngeal Wall: Local Control (Washington University, St. Louis)

	Local Control			
Treatment	T1	T2	T3	T4
Surgery*	6/8	7/12	4/12	0/1
Radiation therapy alone	1/1	3/6	0/5	1/1

* Twenty-nine patients had preoperative radiation therapy: two hod postoperative radiation therapy; and two had surgery.
(Adapted with permission from Marks JE, Freeman RB, Lee F, Ogura JH. Pharyngeal wall cancer: an analysis of treatment results, complications, and patterns of failure. Int J Radiat Oncol Biol Phys 1978;4:588. Copyright © 1978, Pergamon Press, Ltd)

the 3-year actuarial survival rate was 17% and the 3-year absolute survival rate was 14%. An operative mortality rate of 14% and a high risk of major surgical complications offset any gain in local control.

A group of 25 patients (5 with stage T2 disease, 20 with stage T3 or T4 disease) were managed at M. D. Anderson Hospital by combined surgery and radiation therapy.[16] Nineteen received postoperative radiation therapy. Seven had positive margins, and three had close margins. Fifteen patients were dead at 5 years (6 of local recurrence or neck recurrence, 5 of distant metastasis, 1 of intercurrent disease, and 3 of uncertain causes). The 5-year absolute survival rate was 4 of 19 (21%).

Pyriform Sinus

Radiation Therapy

Most reports paint a rather dismal outlook for pyriform sinus tumors treated by radiation therapy alone.[9,20] Kirchner and Owen reported only two 3-year survivors of 55 patients treated by radiation therapy alone; all but 4 patients had advanced disease.[9]

El-Badawi and coworkers reported results for 48 patients treated with ^{60}Co.[7] Fifty-six percent had T1 and T2 lesions; in 65% the disease was staged N2 or N3. Eleven patients had a radical neck dissection after radiation therapy. Eleven (23%) developed a failure above the clavicles. Forty-eight percent were free of disease at 2 years. One patient died of pharyngeal necrosis.

In 1987, Mendenhall and associates updated the University of Florida results for 54 patients treated with radical irradiation (Tables 20-5 through 20-8).[13] Nearly all T1 lesions were treated by radiation therapy; T2 and T3 lesions were irradiated if they were exophytic and in the upper pyriform sinus or if the patient refused operation. T2 lesions with impaired vocal cord mobility have approximately 20% poorer local control compared with T2 lesions with normal mobility. All T4 lesions were irradiated by default; three patients refused surgery and four had medically inoperable lesions.

Four patients with local failure were salvaged by surgery. Two were alive, free of disease, at 7 and 9 years, and two died of intercurrent disease at 4 years. Treatment failed in only four patients because of failure to control neck disease. The local control rate (1978 to 1991) for patients treated with twice-a-day fractionation is nine of nine T2 lesions and two of three T3 lesions (Parsons JT, personal communication, March 1991). The appearance of the larynx and pyriform sinus for two patients at 7 and 15 years after radiation therapy is shown in Figures 20-20 and 20-21.

Stage IV includes a favorable group (IVA) with small primary lesions (T1 or T2) and N2 or N3A neck disease, which can often be successfully managed by irradiation followed by a neck dissection. In this group, the 2- and 5-year cause-specific disease-free survival was similar to that for stage III.

Partial Laryngopharyngectomy

The results of treatment are given in Table 20-9 for 80 patients with carcinoma of the pyriform sinus treated at Washington University in St. Louis by 3000 cGy of preoperative radiation followed by partial laryngopharyngectomy.[12] Seventy patients had the equivalent of AJCC T1 lesions, with disease limited to the pyriform sinus, and 10 patients had disease extending beyond the pyriform sinus. The cause of death was cancer in 26%; there were complications of treatment in 14% and intercurrent disease in 20%. The 2-year absolute survival rate was 56%, and the 5-year absolute survival rate was 38% (Marks JE, written communication, May 1980).

Laryngopharyngectomy

The results of treatment for 57 patients treated by preoperative radiation therapy followed by total laryngectomy and partial pharyngectomy were shown in Ta-

TABLE 20-5. Pyriform Sinus Carcinoma: Local Control (No. Controlled/No. Treated)

T Stage	Excluded*	Once-a-Day Fractionation	Twice-a-Day Fractionation	Total Local Control With Radical Radiation Therapy	No. Salvaged/ No. Attempts	Ultimate Local
T1	2	8/9	No data	8/9	0/0	8/9
T2	10	12/16	3/4	15/20	3/4	18/20
T3	2	1/3	1/2	2/5	1/2	3/5
T4	2	0/2	0/2	0/4	0/1	0/4

* All potients were treated with continuous-course irradiation; 13 patients treated with a planned split-course technique were not included in this study.
(Mendenhall WM, Parsons JT, Cassisi NJ, Million RR. Squamous cell carcinoma of the pyriform sinus treated with radical radiation therapy. Radiother Oncol 1987;9:202)

TABLE 20-6. Pyriform Sinus Carcinoma: Control of the Clinically Positive Hemineck (No. Controlled/No. Treated)*

Stage	Irradiation Alone	Irradiation and Neck Dissection
N1	6/6	1/1
N2A	1/2	3/3
N2B	3/3	5/6
N3A	0/2	1/2

* Patients continuously disease-free at the primary site.
(Mendenhall WM, Parsons JT, Cassisi NJ, Million RR. Squamous cell carcinoma of the pyriform sinus treated with radical radiation therapy. Radiother Oncol 1987;9:203)

ble 20-9. Thirty-five patients had lesions confined to the pyriform sinus (AJCC T1), and the remainder had extension beyond the pyriform sinus (AJCC T2 to T4). The cause of death was cancer in 56%, complications of treatment in 11%, and intercurrent disease in 18%.

El-Badawi and coworkers presented results for 203 patients treated by surgery alone and 125 patients treated by surgery (total laryngopharyngectomy) followed by 6000 cGy of postoperative radiation therapy (as well as 17 patients who had surgery after 4500 to 5000 cGy preoperative radiation therapy) (Table 20-10).[7] The stages in the three groups were comparable. There was a minimum follow-up of 4 years. The actuarial survival of the two large groups is shown in Figure 20-22. For the

TABLE 20-7. Pyriform Sinus Carcinoma: Control Above the Clavicles (No. Controlled/No. Treated)

Modified AJCC Stage	Excluded*	Control With Initial Treatment	No. Salvaged/ No. Attempts	Ultimate Control
I	0	1/1	0/0	1/1
II	1	5/6	1/1	6/6
III	3	5/10	1/2	6/10
IVA	6	12/16†	1/2	13/16‡
IVB	2	1/9†	0/2	1/9‡

* All patients were treated with continuous-course irradiation; 13 patients treated with a planned split-course technique were not included in this study.
† 12/16 vs. 1/9, $P = .003$.
‡ 13/16 vs. 1/9, $P = .001$.
(Mendenhall WM, Parsons JT, Cassisi NJ, Million RR. Squamous cell carcinoma of the pyriform sinus treated with radical radiation therapy. Radiother Oncol 1987;9:204)

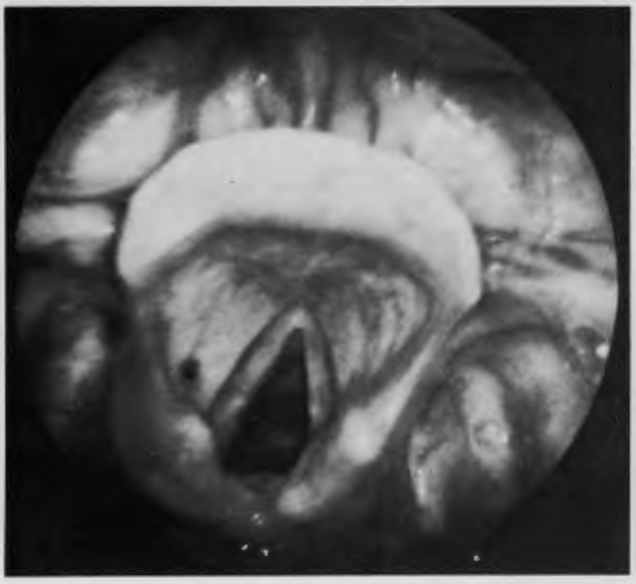


Figure 20-20. Appearance of pyriform sinus 7 years after radiation therapy and right radical neck dissection for squamous cell carcinoma of the right pyriform sinus (T2N3B [N2B, N1]).

Figure 20-21. Appearance of pyriform sinus 15 years after radiation therapy and right radical neck dissection for squamous cell carcinoma of the right pyriform sinus (T2N1).

TABLE 20-8. Pyriform Sinus Carcinoma: 5-Year Survival (No. Alive/No. Treated)

Modified AJCC Stage	5-Year Absolute Survival	5-Year Cause-Specific Survival
I	1/1	1/1
II	3/5	3/3
III	5/13	5/8
IVA	7/17*	7/12†
IVB	2/10*	2/8†

* 7/17 vs. 2/10, $P = .187$.
† 7/12 vs. 2/8, $P = .132$.
(Mendenhall WM, Parsons JT, Cassisi NJ, Million RR. Squamous cell carcinoma of the pyriform sinus treated with radical radiation therapy. Radiother Oncol 1987;9:205)

group given postoperative radiation therapy, the improvement in survival at 5 years was 15 percentage points. Note that the 22% actuarial 5-year survival rate for low-dose preoperative radiation therapy and total laryngopharyngectomy (see Table 20-9) is identical to that for surgery alone (see Fig. 20-22). The rate of failure above the clavicles in the two groups is likewise almost identical (37% versus 39%). Mendenhall and associates reviewed the University of Florida experience for 85 patients managed by total laryngectomy and partial pharyngectomy and 3 patients managed by partial laryngopharyngectomy and compared the results to patients managed by radical radiation therapy with or without planned neck dissection. Seventy-two of the surgical patients had either preoperative radiation therapy (35 patients) or postoperative radiation therapy (37 patients) (Tables 20-11 through 20-16).[14]

TABLE 20-9. Carcinoma of the Pyriform Sinus: Results of Treatment by Preoperative Radiation Therapy Plus Partial Laryngopharyngectomy (PLP) or Preoperative Radiation Therapy Plus Total Laryngectomy and Partial Pharyngectomy (TLP)

Result	PLP (80 Patients*)	TLP (57 Patients†)
Local recurrence ± neck recurrence	14%‡	14%
Neck recurrence ± distant metastases (primary lesion controlled)	9%	23%
Distant metastases alone	11%	21%
5-year actuarial survival (no evidence of disease)	40%	22%

* T1, 70 patients; T2–T4, 10 patients (AJCC staging).
† T1, 35 patients; T2–T4, 22 patients (AJCC staging).
‡ Four patients were salvaged after initial treatment failure.
Note: Washington University, St. Louis, data 1964–1974.
(Data from Marks JE, Kurnik B, Powers WE, Ogura JH. Carcinomo of the pyriform sinus: an analysis of treatment results and patterns of failure. Cancer 1978;41:1008–1015)

TABLE 20-10. Carcinoma of the Pyriform Sinus: Results of Treatment

Treatment Modality	Patients	Failure Above Clavicles (%)	2-Year NED (%)	Cause of Death (>2 Years)
Surgery	203	39*	40†	DM—8 ID—23
Surgery and postoperative irradiation	125	11*	50†	N—1 DM—6 ID—7
Preoperative irradiation and surgery	17	29	47	DM—2 ID—2

NED, no evidence of pyriform sinus cancer; DM, distant metastasis; ID, intercurrent disease; N, neck nodes.
* $P = <.001$.
† $P = .04$.
Note: M. D. Anderson Hospital data; patients treated 1949–1976; analysis January 1981.
(Adapted from El-Badawi SA, Goepfert H, Fletcher GH, Herson J, Oswald MJ. Squamous cell carcinoma of the pyriform sinus. Laryngoscope 1982;92:360)

TABLE 20-11. Pyriform Sinus Carcinoma: Local Control After Initial Treatment in 103 Patients* (No. Controlled/No. Treated)

T Stage	Radiotherapy ± Neck Dissection†	Surgery ± Radiotherapy	Significance Level
T1	11/14 (79%)	1/1	.800
T2	15/21 (71%)	3/5	.498
T3	3/7	29/39 (74%)	.113
T4	1/8	5/8	.059

* Fifty-two patients who died within 2 years of treatment in whom the primary site had been continuously free of disease were excluded from this analysis.
† Includes patients treated by split-course irradiation.
(Mendenhall WM, Parsons JT, Devine JW, Cassisi NJ, Million RR. Squamous cell carcinoma of the pyriform sinus treated with surgery and/or radiotherapy. Head Neck Surg 1987;10:89)

TABLE 20-12. Pyriform Sinus Carcinoma: Ultimate Local Control in 103 Patients* (No. Controlled/No. Treated)

T Stage	Radiotherapy ± Neck Dissection†	Surgery ± Radiotherapy	Significance Level
T1	11/14 (79%)	1/1	.800
T2	18/21 (86%)	3/5	.236
T3	4/7	30/39 (77%)	.255
T4	1/8	5/8	.059

* Includes patients successfully salvaged after treatment failure. Fifty-two patients who died within 2 years of treatment in whom the primary site had been continuously free of disease were excluded from this analysis.
† Includes patients treated by split-course irradiation.
(Mendenhall WM, Parsons JT, Devine JW, Cassisi NJ, Million RR. Squamous cell carcinoma of the pyriform sinus treated with surgery and/or radiotherapy. Head Neck Surg 1987;10:90)

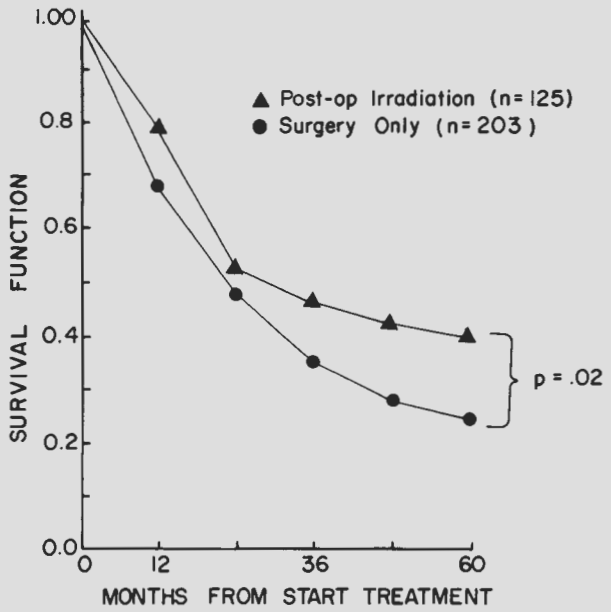


Figure 20-22. Carcinoma of the pyriform sinus: actuarial survival comparing surgery only and surgery plus postoperative radiation therapy (M. D. Anderson Hospital data, 1949–1976, minimum follow-up 4 years). (Redrawn from El-Badawi SA, Goepfert H, Fletcher GH, Herson J, Oswald MJ. Squamous cell carcinoma of the pyriform sinus. Laryngoscope 1982;92:361)

FOLLOW-UP POLICY

Posterior Pharyngeal Wall

Ulceration is the hallmark of radiation failure, although two patients have been observed with persistent ulceration that represented a soft tissue necrosis that eventually healed. Radiation failures, usually small localized recurrences, can occasionally be salvaged by pharyngectomy.

Patients with pharyngeal wall lesions are at high risk for esophageal and lung cancers, and these areas should be monitored with chest roentgenography and barium swallow.

Pyriform Sinus

Patients irradiated for cure must have follow-up examinations every 4 to 6 weeks for 2 years to detect recurrence as early as possible. The hallmark of persistence or recurrence is major edema of the arytenoids, pain referred to the ear or when swallowing, and development of hoarseness and a fixed cord. Patients who continue to smoke and drink make assessment more difficult. The addition of a radical neck dissection increases the edema; mild to moderate edema that is stable or slowly regressing without pain, however, is usually safe to follow. Direct laryngoscopy may be necessary if indirect

TABLE 20-13. Pyriform Sinus Carcinoma: Control Above the Clavicles After Initial Treatment in 121 Patients* (No. Controlled/No. Treated)

Modified AJCC Stage	Radiotherapy ± Neck Dissection†	Surgery ± Radiation therapy	Significance Level
I	3/4	1/1	.800
II	5/6	No data	
III	7/14 (50%)	15/22 (68%)	.230
IVA	12/17 (71%)	11/20 (55%)	.263
IVB	2/14 (14%)	7/23 (30%)	.241

* Thirty-four patients who died within 2 years of treatment in whom the primary site and neck had been continuously free of disease were excluded from this analysis.
† Includes patients treated by split-course irradiation.
(Mendenhall WM, Parsons JT, Devine JW, Cassisi NJ, Million RR. Squamous cell carcinoma of the pyriform sinus treated with surgery and/or radiotherapy. Head Neck Surgery 1987;10:90)

TABLE 20-14. Pyriform Sinus Carcinoma: Ultimate Control Above the Clavicles in 121 Patients* (No. Controlled/No. Treated)

Modified AJCC Stage	Radiation therapy ± Neck Dissection†	Surgery ± Radiotherapy	Significance Level
I	3/4	1/1	.800
II	6/6	No data	
II	9/14 (64%)	16/22 (73%)	.431
III	13/17 (76%)	11/20 (55%)	.154
IVA	2/14 (14%)	7/23 (30%)	.241

* Includes patients successfully salvaged after treatment failure. Thirty-four patients who died within 2 years of treatment in whom the primary site and neck had been continuously free of disease were excluded from this analysis.
† Includes patients treated by split-course irradiation.
(Mendenhall WM, Parsons JT, Devine JW, Cassisi NJ, Million RR. Squamous cell carcinoma of the pyriform sinus treated with surgery and/or radiotherapy. Head Neck Surgery 1987;10:90)

TABLE 20-15. Pyriform Sinus Carcinoma: Cause-Specific 5-Year Survival by AJCC Stage in 103 Patients* (No. Alive/No. Treated)

Modified AJCC Stage	Radiotherapy ± Neck Dissection†	Surgery ± Radiotherapy	Significance Level
I	3/4	No data	—
II	3/3	No data	—
III	6/11 (55%)	7/17 (41%)	.380
IVA	7/13 (54%)	5/19 (26%)	.114
IVB	2/12 (17%)	3/24 (12%)	.549

* Patients died secondary to treatment complications were coded as dead of disease; 52 other patients who died within 5 years of treatment with no recurrence of cancer were excluded from the analysis.
† Includes patients treated by split-course irradiation.
(Mendenhall WM, Parsons JT, Devine JW, Cassisi NJ, Million RR. Squamous cell carcinoma of the pyriform sinus treated with surgery and/or radiotherapy. Head Neck Surgery 1987;10:91)

TABLE 20-16. Pyriform Sinus Carcinoma: Cause-Specific 5-Year Survival by T Stage in 103 Patients* (No. Alive/No. Treated)

T Stage	Radiotherapy ± Neck Dissection†	Surgery ± Radiotherapy	Significance Level
T1	7/12 (58%)	0/1	.462
T2	11/18 (61%)	2/5	.367
T3	3/6	12/38 (32%)	.327
T4	0/7	1/16 (6%)	.696

* Patients dead secondary to treatment complications were coded as dead of disease; 52 other patients who died within 5 years of treatment with no recurrence of cancer were excluded from the analysis.
† Includes patients treated by split-course irradiation.
(Mendenhall WM, Parsons JT, Devine JW, Cassisi NJ, Million RR. Squamous cell carcinoma of the pyriform sinus treated with surgery and/or radiotherapy. Head Neck Surg 1987;10:91)

examination is not satisfactory, but biopsies are not recommended unless recurrence is suspected.

A recurrence after combined treatment can rarely be salvaged, but a recurrence after surgery alone may be salvaged by radiation therapy or combined surgery and radiation therapy.

COMPLICATIONS OF TREATMENT

Pharyngeal Wall

Surgical Complications

Cunningham and Catlin reported an operative mortality rate of 9% and a complication rate of 57% for patients operated on during the period 1951 to 1961.[6] Mucocutaneous fistula was the most common problem.

Marks and coworkers reported a 14% operative mortality rate plus major complications including pharyngocutaneous fistula (31%) and carotid rupture (14%) for patients treated with preoperative radiation therapy, 2500 to 3000 cGy.[11]

Radiation Therapy Complications

Meoz-Mendez and associates analyzed the complications for 164 patients with carcinoma of the pharyngeal wall treated by radiation therapy alone.[16] There was a 5% incidence of fatal complications. In 7 patients, the fatality was secondary to carotid rupture, associated with attempts at surgical salvage. Severe laryngeal edema developed in only 2 patients. Radiation myelitis was documented in 2 patients. The overall incidence of radiation therapy-related complications was 12% and increased in patients with advanced lesions.

Mendenhall and associates reported eight severe complications of 75 tumors irradiated.[15] The incidence of severe complications by stage was as follows: I, 0 of 2; II, 1 of 16; III, 2 of 22; IVA, 2 of 14; IVB, 3 of 20. Four patients developed inability to swallow requiring a permanent gastrostomy tube. One patient developed severe laryngeal edema that required a permanent tracheostomy. One patient developed a unilateral vocal cord palsy, Horner's syndrome, brachial plexopathy, and a stricture requiring a permanent gastrostomy; although recurrent disease was initially suspected, this patient survived for 5 years after treatment, without evidence of recurrent cancer, before dying of intercurrent disease. Finally, two patients developed severe soft tissue necrosis of the posterior pharyngeal wall, which was fatal in a patient with a T4 lesion.

Pyriform Sinus

Surgical Complications

The complications of partial laryngopharyngectomy include a 12% operative mortality rate, pharyngocutaneous fistula, carotid rupture, aspiration, and dysphagia.[12] The morbidity is higher after preoperative radiation therapy.

The complications of total laryngopharyngectomy include a treatment-related mortality rate of 11%, fistula, carotid rupture, and pharyngeal stenosis.[12]

The complication rate is increased by the addition of radiation therapy.[5] Attempted surgical salvage of radiation therapy failures has a significant operative morbidity and mortality in the best of hands, but a few cures are produced. Pharyngocutaneous fistula and exposure of the carotid vessels are life-threatening complications.

Radiation Therapy Complications

Lymphedema of the larynx occurs temporarily in most cases and is increased by radical neck dissection. The edema gradually resolves in 2 to 6 months in successfully treated cases and may last for a year if bilateral neck dissection is added. A major complication of radiation therapy is laryngeal necrosis.

Mendenhall and coworkers reviewed the complications in 54 patients treated by radical irradiation.[13] Six patients (11%) developed severe complications secondary to radiation therapy. Two developed a laryngeal chondronecrosis, necessitating a total laryngectomy in one patient and a permanent tracheostomy in the other. One patient developed severe laryngeal edema necessitating a permanent tracheostomy. Another patient developed severe laryngeal edema; he subsequently underwent direct laryngoscopy and biopsy at another institution with equivocal findings and then underwent a total laryngectomy—partial pharyngectomy with no tumor noted in the specimen. One patient developed laryngeal edema (requiring a temporary tracheostomy), inability to swallow (necessitating a temporary gastrostomy), and bilateral 12th cranial nerve palsies. Another patient developed inability to swallow, without evidence

TABLE 20-17. Pyriform Sinus Carcinoma: Incidence of Severe Complications in 155 Patients

Treatment Group (No. Patients)	Severe Complications After Initial Treatment	No. Severe Complications/ No. Salvage Operations Attempted	Total Severe Complications	Total Treatment Mortality
Radiation therapy ± neck dissection (67)	10%	7/15 (47%)	21%	6%
Surgery alone (16)	50%	0/1	50%	6%
Preoperative radiation therapy + surgery (35)	37%	0/1	37%	9%
Surgery + postoperative radiation therapy	24%	No data	24%	0%

(Mendenhall WM, Parsons JT, Devine JW, Cassisi NJ, Million RR. Squamous cell carcinomo of the pyriform sinus treated with surgery and/or radiotherapy. Head Neck Surg 1987;10:91)

of a stricture, that necessitated chronic hyperalimentation owing to a history of prior gastric surgery. All but one of the complications occurred at doses of 7000 to 7500 cGy. All six patients who developed severe complications had T2 primary lesions and were treated with once-a-day fractionation.

Four patients developed postoperative complications after a planned neck dissection. Three patients developed relatively minor wound breakdowns, and one lost part of a pectoralis major flap and had to have a second surgical procedure for a deltopectoral flap.

Seven patients underwent salvage total laryngectomy and partial pharyngectomy for local recurrence after radical irradiation. Four of seven patients developed severe postoperative complications: wound breakdown (three patients), pharyngocutaneous fistula (one patient), and carotid blowout (one patient).

Complications of Combined Surgery and Radiation Therapy

The incidence of severe complications for combined therapy, including those added by attempted salvage procedures, is given in Table 20-17.

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21

CARCINOMA OF THE CERVICAL ESOPHAGUS

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The incidence of esophageal cancer varies geographically, ranging from 130.8 per 100,000 people in Iran to 0.5 per 100,000 people in Nigeria. The age-specific incidence rates in the Gonbad region of Iran for people 35 to 64 years of age are 262.9 per 100,000 for women and 206.4 per 100,000 for men.[68] The adjusted average incidence in Linhsien county of Northern China is 108.56 per 100,000.[80] The average age-adjusted incidence rates of cancer of the esophagus in the United States from 1973 to 1977 were 4.8 and 1.6 for white men and women, and 16.9 and 4.5 for black men and women, respectively.[68] It was estimated that 11,300 cases of esophageal cancer would be diagnosed in the United States in 1993.[9]

Esophageal cancer is particularly common in black men in the coastal regions of North Carolina and South Carolina, Georgia, and northeast Florida. In addition, inhabitants of Puerto Rico have a high incidence of esophageal carcinoma. Cancer of the cervical portion of the esophagus is relatively rare, comprising 3.6% to 33% of all esophageal cancer. In a series of 1212 patients with esophageal cancer, Yin and coworkers[81] reported the location of disease as follows: cervical, 44 (3.6%); upper-third thoracic, 282 (23.3%); middle-third thoracic, 742 (61.2%); and lower-third thoracic, 144 (11.9%). In contradistinction to cancers of the thoracic esophagus and other head and neck sites, malignancies of the cervical esophagus are more common in women, with a female-to-male ratio varying from 5:1 to 1:1. Patients are usually in the older age-group, with most presenting in their 50s and 60s. The disease occurs more frequently in patients with a history of excessive alcohol ingestion (whiskey drinkers more so than heavy beer or wine drinkers), cigarette smoking, a previous head and neck cancer (up to 20%), or the Plummer-Vinson syndrome (long-standing dysphagia, anemia, atrophy of mucous membranes, and brittle nails).[68] The Plummer-Vinson syndrome is thought to be secondary to a nutritional deficiency and is seen more commonly in Scandinavian and British women. Esophageal cancer is also associated with tylosis, celiac disease, lye stricture, and the presence of nitrosamines and their precursors in food and drinking water.[26,27,80]

ANATOMY

The cervical esophagus is simply a narrow, inferior extension of the pharynx. It begins at the cricopharyngeus at the level of C6 (about 16 cm from the incisors), is 6 to 8 cm in length, and arbitrarily ends at the thoracic inlet (about 23 cm from the incisors), where it is continuous with the thoracic esophagus opposite the upper border of the manubrium (T4). No anatomic change in the esophagus per se occurs at this transition. As it descends in the neck, it deviates slightly to the left beyond the border of the overlying trachea. It is related to the trachea and recurrent laryngeal nerve on its anterior aspect, to the thyroid gland and carotid sheath laterally, and to the retroesophageal space and prevertebral fascia posteriorly. It is composed of squamous epithelium and two muscle layers: (1) an inner circular layer, and (2) an outer longitudinal layer. There is no serosa.

The cervical esophagus receives its blood supply from the inferior thyroid artery and vein. Two sets of capillary lymphatics exist: one arising in the submucosa of the esophagus, and the other in the muscular wall. The one in the submucosa is more important, having fairly large capillaries, which are continuous with those of the pharynx above. The muscular capillary network is composed of delicate capillaries, and is less important in tumor spread.

The collecting vessels originating in the submucosal tissue either traverse the muscularis and empty into the nearest lymph nodes, or ascend or descend vertically beneath the mucosa for some distance before traversing the muscularis. The vessels in the cervical esophagus ascend,

as do those in the upper portion of the thoracic esophagus. Because of this arrangement, metastases may occur in a nearby or neighboring node, or may occur in a lymph node placed at some distance from the origin of the capillary lymphatic. The lymphatic network of the upper end of the esophagus is diverted partly into the network of the pharynx, and ascends along the pyriform recesses and enters the collecting tracts of the larynx and pharynx. These vessels traverse the thyrohyoid membrane and terminate in the various nodes of the internal jugular chain. The primary nodes for the cervical esophagus are the right and left lateral paratracheal nodes (the nodes which lie in the groove between the esophagus and trachea alongside the recurrent laryngeal nerve) and the internal jugular chain nodes. Since the general lymphatic flow in the upper esophagus is upward, lymph nodes normally should appear either at the level of the cancer in the esophagus or above it. At least some of the collecting vessels terminate in the cervical lymph nodes.

PATHOLOGY

About 95% of esophageal cancers are squamous cell carcinomas, 4% are adenocarcinomas, and other histologic types represent less than 1% of the total.[10,24,68] Most adenocarcinomas occur in the distal esophagus. Some of the infrequently observed neoplasms that may occur in the esophagus include minor salivary gland tumors, sarcomas, undifferentiated carcinomas, and pseudosarcomas. The histologic diagnosis in 34 cervical esophageal lesions treated with irradiation at the University of Florida (Gainesville) was squamous cell carcinoma in 32, high-grade mucoepidermoid carcinoma in one, and adenosquamous carcinoma in one.[50]

NATURAL HISTORY AND PATTERNS OF SPREAD

Carcinomas of the esophagus arise from the surface epithelium and represent the end stage of the spectrum that includes dysplasia and carcinoma in situ. The time required for a lesion to progress from severe dysplasia to massive carcinoma, and the percentage of dysplastic lesions that do so, are not well defined and vary from one geographic area to another. It has been estimated that it may take 7 to 8 years to progress from esophagitis through dysplasia to carcinoma in situ, and another 3 to 4 years for carcinoma in situ to develop into advanced cancer.[40] The time course may be shorter in some areas, such as Iran.[40]

Submucosal and skip spread of the primary tumor beyond its gross extent is characteristic of cancer of the esophagus. Kakegawa and coworkers[33] reported that 19% of 64 patients with carcinomas of the cervical esophagus had evidence of intramural skip metastases on pathologic examination of the esophagectomy specimens. Because most of these patients received preoperative radiation therapy, this probably represents an underestimate of the true incidence of submucosal extension. It has been reported to occur up to 8 cm from the edge of the obvious primary lesion.[30] As the tumor enlarges, it extends to contiguous structures such as the hypopharynx, larynx, trachea, thyroid gland, recurrent laryngeal nerve, and great vessels. Large blood vessels, usually arteries, may be encased by tumor; veins are more often compressed.

The incidence of lymph node metastasis reported for the entire esophagus is related to the length of the primary lesion, with 50% of lesions less than 5 cm in length having lymph node metastases, compared with 90% when the primary lesion is longer than 5 cm.[64] The distribution of lymph node metastases in an autopsy series for carcinoma of the upper third of the esophagus was supraclavicular and infraclavicular, 7%; paratracheal and paraesophageal, 84%; mediastinal, 28%; and abdominal, 11%.[16a] The incidence of clinically positive lymph nodes in the neck at presentation at the University of Florida[50] was 18% (6 of 34) for carcinoma of the cervical esophagus. The lymph node metastases may be located at any level in the neck, including the subdigastric nodes, but are most commonly found in the lower jugular chain. A deep medial mass in the low neck may be a direct extension of the primary lesion. Once the tumor has extended to the postcricoid area and pyriform sinus, it spreads through the lymphatic pathways in a manner similar to primary cancer in those locations, and therefore reaches the jugulodigastric lymph nodes without necessarily involving lymph nodes in the low jugular chain. Two cases have been followed in which there was tumor recurrence in lymph nodes in the upper neck, just above the irradiation portal.

Distant metastasis is frequent, involving primarily the liver and the lung.[5] The approximate frequencies, based on an autopsy series, are liver, 16%; lung or pleura, 31%; bone, 9%; kidney, 4%; and adrenals, 2%.[16]

Various parameters that may influence the prognosis of patients with esophageal carcinoma are discussed briefly.

The prognosis for women with esophageal cancer is better than for men.[19,36,55] Age has been reported by some investigators to have no influence on survival after treatment, and has been reported by others to have a significant impact on the 5-year survival rate. It is likely that if one corrected for extent of disease and death secondary to intercurrent disease, age would have little impact on prognosis, except that the very elderly might not tolerate an aggressive course of treatment as well as younger patients.

The influence of tumor site on prognosis is dependent, in part, on the treatment modality employed. In general, patients with distal esophageal cancer fare better with surgery, and radiation therapy alone yields better results for patients with proximal lesions. The macroscopic appearance of the tumor has been reported to be of prognostic value with exophytic, fungating lesions having a better prognosis than ulcerative, infiltrative tumors.[22] The degree of obstruction at diagnosis, which is a reflection of tumor size, also has been reported to influence the 5-year survival rate.[23] The length of the lesion, too, has been found to significantly influence survival.[23,25] Both the depth of tumor penetration through the esophageal wall and regional lymph node involvement have been found to exert a marked impact on 5-year survival rates.[8,23,25,36,51,62,69]

Patients with histologically well-differentiated carcinomas reportedly have an improved survival rate compared with those with moderately or poorly differentiated lesions.[36] Additionally, pathologic evidence of lymphatic invasion, vascular space invasion, or blood vessel invasion is thought to adversely influence prognosis.[73]

CLINICAL PICTURE

Symptoms

Dysphagia and weight loss, the two most common symptoms, are present in almost all patients at the time of diagnosis. These symptoms occur earlier than with lesions of the hypopharynx because the lumen of the cervical esophagus is smaller. Less frequently, patients present with dyspnea, malaise, hoarseness (secondary to direct extension to the larynx or the recurrent laryngeal nerve), pain, cough, excess secretions, vomiting, and hematemesis. Patients with cancer of the cervical esophagus present with relatively early lesions compared with those with cancer of the thoracic esophagus.

Physical Findings

In addition to weight loss, the physical findings secondary to the lesion in the cervical esophagus include pooling of saliva in the pyriform sinus, visible tumor extending into the hypopharynx, direct extension into the soft tissues of the neck, loss of the thyroid click, anterior bowing of the trachea, fullness in the midline of the lower neck, and fixation of a vocal cord. Paratracheal masses may be felt on deep palpation of the lower neck and sternal notch. It is difficult to distinguish between a metastatic lymph node and direct extension of tumor into the neck.

The differential diagnosis of carcinoma of the cervical esophagus includes any lesion arising in the lower neck and superior mediastinum that could invade and obstruct the esophagus. This includes thyroid cancer, lung cancer, thymoma, mediastinal lymphoma, germ cell malignancies, soft tissue sarcoma, and metastatic disease to the regional lymph nodes.

DIAGNOSIS AND STAGING

Biopsy Procedures

Esophagoscopy and biopsy establish the diagnosis of cancer of the cervical esophagus. It is sometimes difficult to establish the diagnosis by esophagoscopy because nondiagnostic tissue is obtained; constriction of the lumen above the lesion may prevent access to tumor, and physicians are reluctant to take deep biopsy samples because of the fear of perforation. Biopsy of a suspicious neck node or mass should be done when indicated. If a biopsy specimen cannot be obtained by endoscopy, cytologic examination of washings from the esophagus may reveal the diagnosis. Computed tomography (CT) directed aspiration biopsy of the esophageal wall, extraluminal tumor, or a tracheoesophageal groove node may prove a safe and effective means of diagnosis in selected cases. Occasionally, a decision must be made to perform surgical exploration for diagnosis. If a lesion is to be treated by radiation therapy alone, patients should be presented with alternatives, and will sometimes opt for treatment without a definitive diagnosis. This situation usually occurs with advanced, incurable lesions when the roentgenographic appearance and the clinical story are sufficient for diagnosis with almost no likelihood of error.

Staging Procedures

Esophagoscopy is used to establish the histologic diagnosis of cancer, as well as to define the location, extent, and mobility of the lesion. Esophagogram also is used to determine the location and extent of the cancer, the degree of obstruction, and the presence of a tracheoesophageal fistula. Tortuosity of the esophagus may indicate fixation to mediastinal structures. A double-contrast esophagogram is preferable to a single-contrast study. Bronchoscopy is used to determine whether the lesion has invaded the trachea. Blood chemistry studies (eg, liver function tests, alkaline phosphatase determination) help to determine if distant metastases are present at the time of diagnosis. The various imaging studies are discussed in the next section.

Diagnostic Imaging

The diagnosis of esophageal cancer may be made by contrast radiologic examination of the esophagus.[75] Small or predominantly submucosal lesions may be missed with conventional fluoroscopic study and spot filming because of the rapid flow of barium through the cervical esophagus. Rapid filming devices (cinefluoroscopic techniques or video tape review) are essential for detecting small lesions and for determining the full extent of larger tumors. If the diagnosis is strongly suspected and fluoroscopic studies produce negative results, CT or magnetic resonance imaging (MRI) should be done. This is especially true if hoarseness and vocal cord dysfunction are present. MRI is preferred in this setting since it can turn up subtle mucosal lesions on T2-weighted images. The studies must be focused on the lower hypopharynx and cervical esophagus, and be as spatially resolved as possible (see Chap. 4).[43]

Normal Anatomy

The normal anatomy of the cervical esophagus on fluoroscopic studies is well known. The mucosa should be smooth and gently folded. Typically, it takes multiple films in several projections during numerous attempts at swallowing to demonstrate the mucosa at the esophageal verge and on to the thoracic inlet, because the lumen is normally collapsed.

The anatomy on CT and MRI is shown in Figures 21-1 and 21-2. On axial CT and MRI, the cervical esophagus appears as a round to elliptical structure, beginning at the lower edge of the cricoid cartilage. On contrast-enhanced CT, a faint rim of mucosal enhancement often is visible centrally, and small amounts of luminal air may be present. On MRI, the esophagus is isointense to other muscular structures, and becomes relatively hypointense to fat on T2-weighted images, with the exception of the central bright mucosa. Mucosal enhancement similar to that on CT is seen when paramagnetic contrast is given. Small vessels normally are visible in the tracheoesophageal groove, but normal nodes usually cannot be distinguished from the vessels on CT or MRI. At the thoracic inlet, the esophagus often will deviate to the left, assuming slightly lobulated morphologic features as it conforms to space between the spine and trachea at the thoracic inlet.

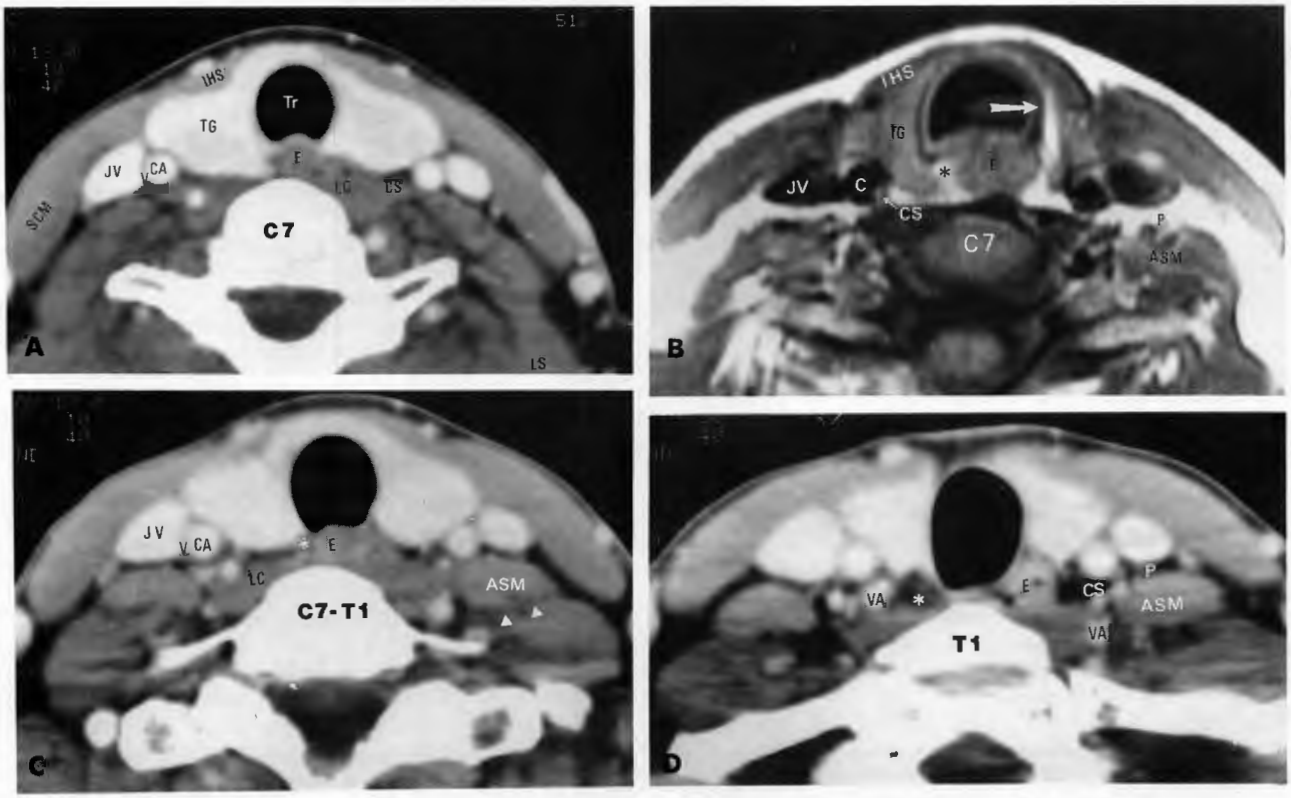

Figure 21-1. The normal anatomy of the cervical esophagus and surrounding structures of the low neck and thoracic inlet are shown. (*A* and *B*) CT and T1-weighted MRI, respectively, made at nearly the same level. (*C* and *D*) CT just above and at the thoracic inlet. SCM, sternocleidomastoid muscle; IHS, infrahyoid strap muscle; ASM, anterior scalene muscle; LC, longus colli muscle; LS, levator scapulae muscle; Tr, trachea; TG, thyroid gland; E, cervical esophagus; CA, carotid artery; JV, jugular vein; VA, vertebral artery; V, position of vagus nerve; P, position of phrenic nerve; CS, position of cervical sympathetic trunk; (*arrow*) tracheal cartilage; (*arrowheads*) positions of trunks of the brachial plexus; *, position of right recurrent laryngeal nerve; C7, seventh cervical vertebral body; T1, first thoracic vertebral body.

Technique of Examination

Standard fluoroscopic techniques using barium may be used to examine the cervical esophagus. Because this area of the esophagus is the one least likely to remain distended for long periods during the examination, it is important to use rapid spot-filming techniques to ensure adequate evaluation of the mucosal surfaces in the collapsed and distended states. Review of videotapes made during swallowing and while at rest is also a useful adjunct to standard fluoroscopic observation. Such review may uncover subtle functional or structural abnormalities suggestive of disease, or at least supportive of a plan for further evaluation with endoscopy or imaging.

CT and MRI should be done in the axial plane with sections no thicker than 3 to 4 mm (5 to 7 mm for T2-weighted MRI) from the top of the cricoid cartilage to at least the upper mediastinum. Intravenous contrast should be used for both examinations; MRI should be done with T1-weighted images before and after contrast infusion. T2-weighted MRI is critical and should be done so that the images are of good quality to clearly define the esophagus (see Fig. 21-2). A receiver coil specifically designed for study of the cervicothoracic junction is required if MRI is to be useful for this region. The study may have to be extended to the middle and lower mediastinum to evaluate the distal extent of tumor or search for mediastinal adenopathy. MRI quality deteriorates somewhat in the chest, and subtle abnormalities confined to the esophageal wall may not be demonstrated.

Indications for Study

The cervical esophagus is studied either to detect a tumor in patients presenting with symptoms of disordered or painful swallowing, or to determine the extent of a known tumor (Fig. 21-3). Sometimes CT, MRI, or fluoroscopic studies are done to evaluate tracheal deviation seen on chest films or palpable low-neck masses. CT and MRI may be necessary to evaluate esophageal displacement or possible masses discovered on fluoroscopic studies.

Once the diagnosis of esophageal carcinoma is made, CT and MRI may be used to define the full extent of intraluminal and extraluminal disease. CT and MRI may show mural involvement extending several centimeters proximal or distal to the visible mucosal extent of the tumor. This tendency reflects the common pathologic

discovery of skip metastases in primary esophageal carcinomas. The extent of submucosal involvement is best appreciated on T2-weighted or contrast-enhanced, T1-weighted images. Extraluminal spread is best evaluated by a combination of MRI and CT (Fig. 21-4). MRI is best for demonstrating tracheal and thyroid gland invasion which has spread to the postcricoid hypopharynx, and the relationship of tumor to the brachiocephalic vessels. CT is better for evaluating nodes and, at times, the status of the thyroid and cricoid cartilages. The best approach is to use MRI first, with CT held in reserve to evaluate the neck and mediastinal nodes and laryngeal skeleton, if necessary. Either study can help differentiate primary tumor from tracheoesophageal groove nodes, but MRI usually is more definitive than CT in this regard.

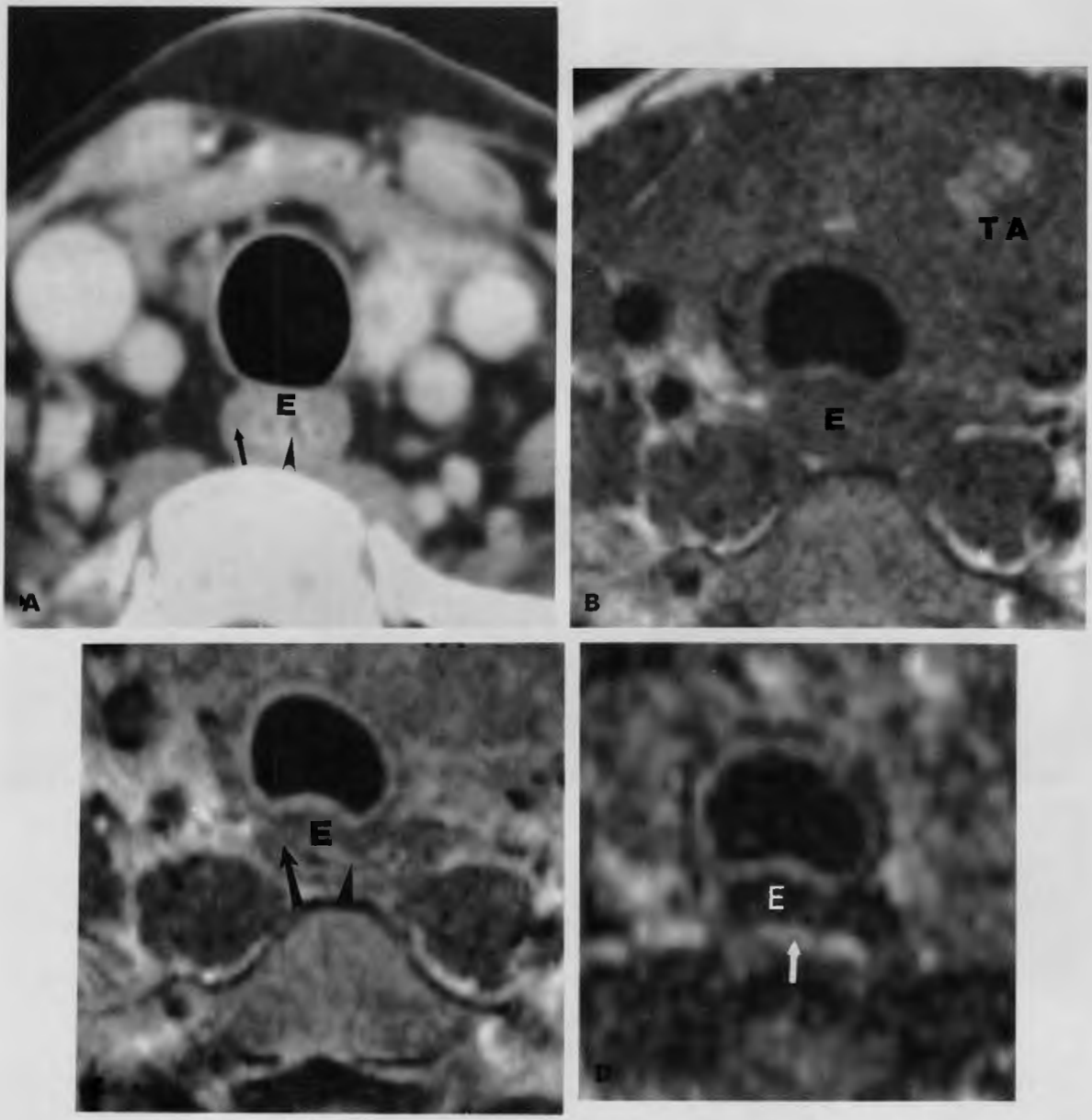

Figure 21-2. Detailed cross-sectional views of the normal cervical esophagus as seen on CT (*A*) and various MRI pulse sequences (*B* through *D*). (*A*) Section from contrast-enhanced CT shows the esophagus (E) as a tissue-density ovoid structure. Its muscular wall (*arrow*) can be distinguished from the collapsed lumen with its enhancing mucosal lining (*arrowhead*). (*B*) T1-weighted MRI without contrast enhancement shows the esophagus (E) as a nondescript ovoid with a signal intensity the same as the neck muscles. (*C*) Contrast-enhanced T1-weighted MRI helps differentiate the muscular wall (*arrow*) of the esophagus (E) from the collapsed lumen with its enhancing mucosa (*arrowhead*); a picture much like that of the CT in (A). TA, thyroid adenoma. (*D*) A heavily T2-weighted MRI image produces the best contrast between the dark muscular wall of the esophagus (E) and the brighter central signal of the luminal contents and mucosa (*arrow*).

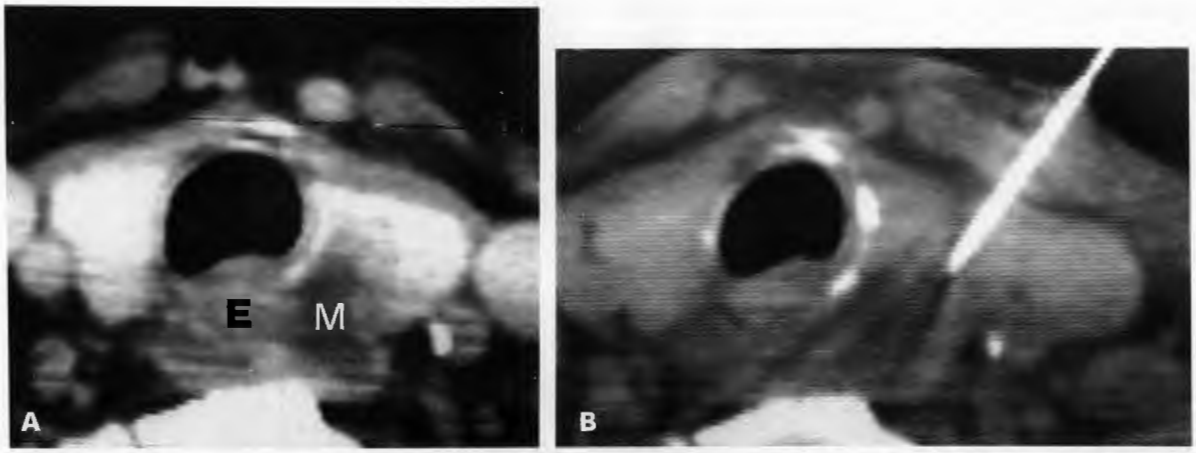

Figure 21-3. A patient with dysphagia had negative barium-swallow results and negative esophagoscopic findings; because of continuing complaints, CT was done. (*A*) CT through the upper cervical esophagus (E) shows it to be enlarged and inseparable from a necrotic mass in the tracheoesophageal groove (M). Repeat esophagoscopy and biopsy gave negative results. (*B*) CT-directed biopsy confirmed squamous cell carcinoma. Surgery confirmed primary esophageal carcinoma and necrotic nodes in the tracheosophageal groove.

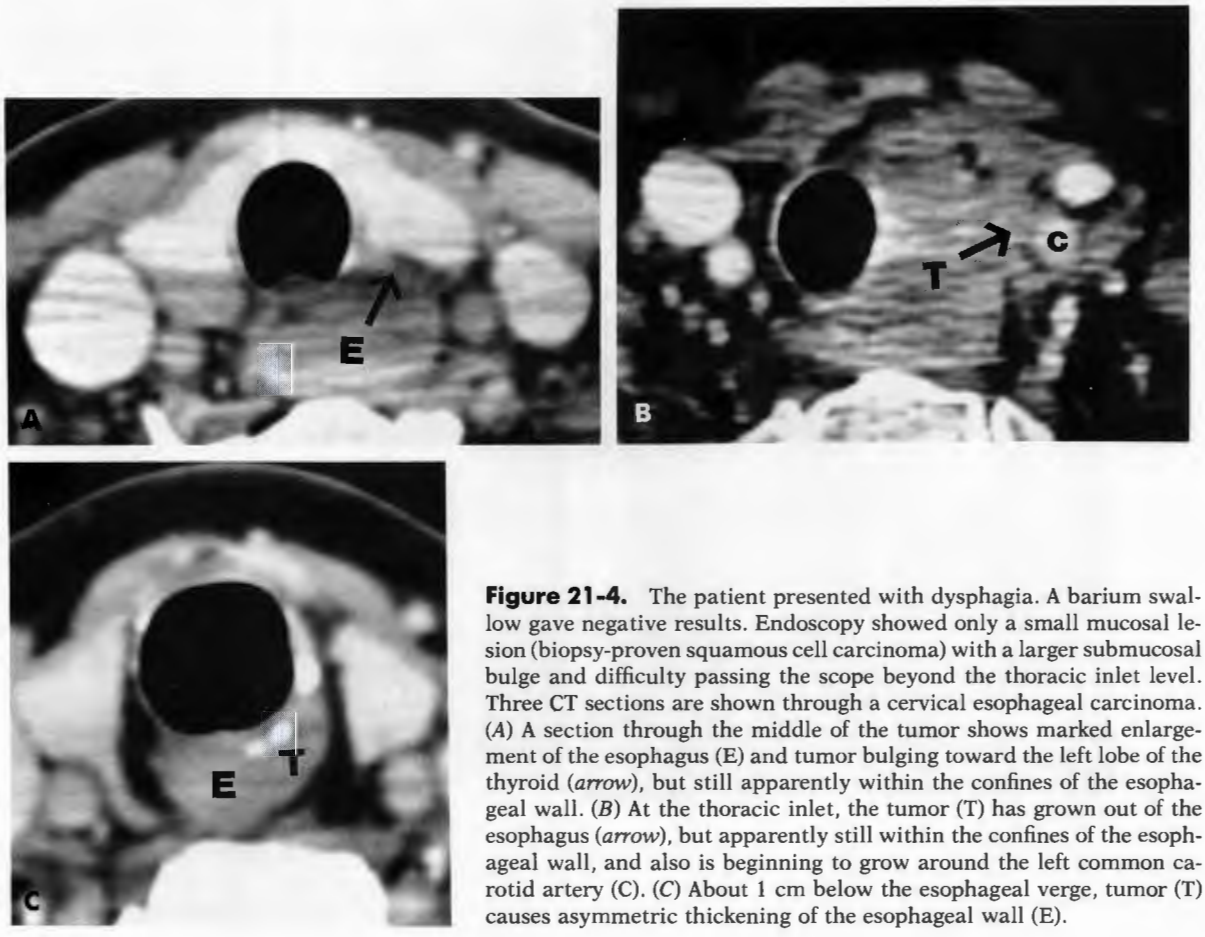

Figure 21-4. The patient presented with dysphagia. A barium swallow gave negative results. Endoscopy showed only a small mucosal lesion (biopsy-proven squamous cell carcinoma) with a larger submucosal bulge and difficulty passing the scope beyond the thoracic inlet level. Three CT sections are shown through a cervical esophageal carcinoma. (*A*) A section through the middle of the tumor shows marked enlargement of the esophagus (E) and tumor bulging toward the left lobe of the thyroid (*arrow*), but still apparently within the confines of the esophageal wall. (*B*) At the thoracic inlet, the tumor (T) has grown out of the esophagus (*arrow*), but apparently still within the confines of the esophageal wall, and also is beginning to grow around the left common carotid artery (C). (*C*) About 1 cm below the esophageal verge, tumor (T) causes asymmetric thickening of the esophageal wall (E).

Contrast-enhanced CT of the chest extended to include the liver, chest roentgenogram, and radionuclide bone scan are used for a metastatic workup when necessary.

Staging

The 1988 American Joint Committee on Cancer (AJCC) staging system for esophageal cancer is listed below.[3]

Primary Tumor

TX: Primary tumor cannot be assessed
T0: No evidence of primary tumor
Tis: Carcinoma *in situ*
T1: Tumor invades lamina propria or submucosa
T2: Tumor invades muscularis propria
T3: Tumor invades adventitia
T4: Tumor invades adjacent structures

Regional Lymph Nodes

NX: Regional lymph nodes cannot be assessed
N0: No regional lymph node metastasis
N1: Regional lymph node metastasis

Distant Metastasis

MX: Presence of distant metastasis cannot be assessed
M0: No distant metastasis
M1: Distant metastasis

Stage Grouping

0: Tis N0 M0
I: T1 N0 M0
IIA: T2 N0 M0 or T3 N0 M0
IIB: T1 N1 M0 or T2 N1 M0
III: T3 N0 M0 or T4, Any N, M0
IV: Any T, Any N, M1

The major differences between the 1983 and 1988 AJCC staging systems are that the 1983[4] T-stages were based on some parameters that could be determined clinically (presence of obstruction, length of tumor, annular involvement), whereas the 1988[3] T-staging is essentially a surgical–pathologic staging system, and the 1988 N-staging for cervical esophageal lesions is less precise. The 1988 staging system is of less use than the 1983 system for clinically staging patients before treatment. A simple clinical staging system for patients with apparently localized disease would be the following: 2 cm, often curable; more than 2 cm but less than or equal to 5 cm, occasionally curable; more than 5 cm, rarely curable.

TREATMENT

Factors in Selection of Treatment Modality

The choice of treatment is between surgical resection, radiation therapy, or a combination of the two.[12,37,46] The addition of adjuvant chemotherapy is controversial. No definite answer exists as to how carcinoma of the cervical esophagus should be managed. The various treatment modalities are discussed to offer a rational treatment approach to patients with cancer of the cervical esophagus.

Surgery

The surgical treatment of cancer of the cervical esophagus is divided into three groups of operations: curative resection, reconstruction, and palliative procedures.[29,53]

Curative Resection

Obviously, the extent of the curative resection will depend on the location and extent of the tumor. It will include a cervical or total esophagectomy with or without an en bloc laryngopharyngectomy.[12,14,21,77] Generally, at least an ipsilateral thyroid lobectomy is included, although some advocate total thyroidectomy because of the high likelihood that the thyroid is involved with tumor. A unilateral or bilateral neck dissection is included if the tumor clinically has metastasized to one or both sides of the neck.[11] Areas of controversy include the use of bilateral elective neck dissection, total versus partial esophagectomy, and routine dissection of the anterior superior mediastinal nodes, which usually entails splitting of the manubrium.[7] The rationale for these more extensive procedures is that cancer of the esophagus exhibits a propensity for lymph node metastasis and submucosal skip lesions. Selection criteria for radical surgery, as outlined by Skinner, include localized disease that is apparently resectable, no hepatic cirrhosis, no severe pulmonary disease, no symptoms of angina or cardiac valvular disease, and no generalized debility for patients older than 70 years of age.[69]

Reconstructive Surgery

A variety of procedures have been proposed to reconstruct the gullet after resection of the cervical esophagus. This attests to the lack of any one procedure that consistently restores continuity to the gullet with an acceptable level of morbidity and mortality. Basically, reconstruction involves one of the following: primary closure[67] or closure with pedicled skin flaps,[77,78] free skin grafts,[15,17,54,63] laryngotracheal allografts,[70,71] free gut grafts, pedicled gut grafts, or, more recently, myocutaneous grafts.[72] Primary closure, pedicled skin grafts, free skin grafts, and laryngotracheal allografts are techniques that are outdated and rarely used. These are not discussed further. The relatively common forms of reconstruction—gut grafts and myocutaneous flaps—are discussed with regard to techniques, advantages, and disadvantages.

MYOCUTANEOUS FLAPS. Various myocutaneous flaps have been used to reconstruct the gullet, and include the deltopectoral flap, the pectoralis major flap, and the latissimus dorsi flap. The deltopectoral flap, described by Bakamjian,[6] is discussed here. The technique involves mobilization of the flap with a blood supply from the internal mammary artery. The flap is formed into a tube, and anastomosis is done to the pharynx superiorly. Anastomosis of the esophageal stump to the side of the skin tube then is performed, and a nasogastric tube is placed through the nose, across the graft, and into the stomach. The inferior aspect of the tube is allowed to remain open (Fig. 21-5). A split-thickness skin graft may

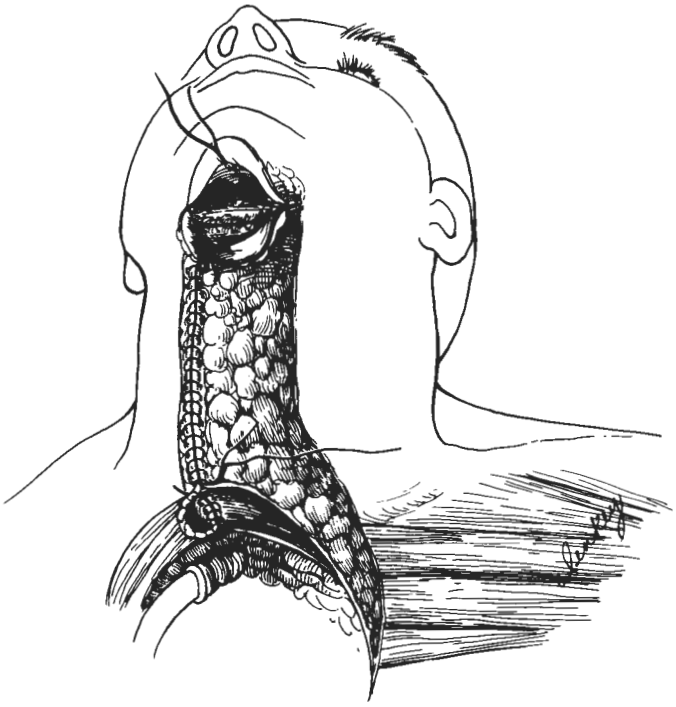

Figure 21-5. Bakamjian deltopectoral flap.

be used to cover any remaining raw areas. The inferior portion of the tube is closed, the nasogastric tube removed, and the inferior part of the flap transected 3 to 5 weeks postoperatively.

This is a well-vascularized, full-thickness flap that is available in sufficient length to bridge the defect. In addition, the flap originates on the chest and, therefore, is not included in the field of irradiation if preoperative treatment is given. A further advantage is that the temporary inferior opening of the tube is below the tracheostomy so that the chance of aspiration is less.

The disadvantages of the use of this flap are that it is bulky and nonperistaltic, a total esophagectomy is not performed, it is a multiple-stage reconstruction, and stenosis and fistula are common complications.[6] Because of the disadvantages outlined above and the availability of better reconstruction alternatives, this technique is rarely used.

FREE GUT GRAFTS. The use of revascularized grafts of either jejunum[13,32,45,65] or sigmoid colon[52] has been reported. The technique using the jejunum is described here. A 10- to 14-cm section of bowel is selected, and the direction of peristalsis is noted. The segment then is resected along with its vascular arcade. The mesenteric vessels selected for anastomosis have a luminal diameter of 3 to 4 mm. The graft may be perfused with a mixture of heparin and Ringer's solution, and anastomosis of the vessels to the superior thyroid artery and internal jugular or common facial vein is then done. The graft is sutured, in an isoperistaltic direction, to the pharynx above and the esophagus below. McKee and Peters[45] have used this graft with or without prior perfusion with Ringer's solution and heparin mixture, and noted no difference in the results.

The advantages of this method of reconstruction are that the lumen of the graft is roughly the same caliber as the esophagus, the length may be tailored to fit the defect, the resection and reconstruction are completed in a single stage, and fistula and stricture are less likely than when skin flaps are used to reconstruct the defect.

It has been stated that when this method of reconstruction is successful, it is very successful, and when it fails, it is a disaster. The disadvantages of this procedure are that a graft necrosis or an anastomotic leak may result in fatal mediastinitis, the entire esophagus is not resected, revascularization is difficult and time consuming, obstruction of the graft may occur,[13] and the bowel is said to be particularly intolerant to postoperative radiation therapy.[7] However, high-dose irradiation (6100 to 6500 cGy) has been given to jejunal graft used to reconstruct the pharynx with no significant increase in treatment complications.[44]

PEDICLED GUT GRAFTS. Two forms of reconstruction using pedicled gut grafts exist: (1) transposition of the stomach, and (2) interposition of the colon with or without the terminal ileum. These techniques are described in turn. The location of the graft may be antethoracic, retrosternal, or posterior mediastinal. The pros and cons of each of these routes are discussed later in the text.

Gastric Transposition. Gastric transposition was described by Ong and Lee in 1960[57] and later by Le Quesne and Ranger[39] and by Harrison.[28] The technique entails mobilization of the stomach with preservation of the right gastric and gastroepiploic vessels. The stomach is then transposed superiorly, usually through the posterior mediastinum, and anastomosis of the fundus to the pharynx is done[28] (Fig. 21-6).

The advantages of this technique are as follows: it is completed in one stage; it has only one anastomosis and that is in the neck; the entire esophagus usually is resected; and the stomach has an excellent blood supply.[57] This is one of the most commonly employed techniques.

The disadvantages of this procedure are that regurgitation occurs; the gastric juices tend to ulcerate adjacent pharyngeal mucosa; the stomach is dislocated from its normal location, so that nutrition may be impaired[12]; the bowel may be intolerant of postoperative radiation therapy[7]; and postoperative mortality is about 10%.[39] Maharaj and coworkers[42] reported a series of eight patients who underwent gastric transposition followed by 6000 cGy over 6 weeks without apparent complications secondary to the radiation therapy.

Colon Interposition. The use of colon to replace the esophagus was initially described independently by Kelling[34] and by Vulliet in 1911.[76] Various parts of the colon and small bowel have been used; the technique that employs the right colon is described here.[11,20] A laparotomy is performed after it is apparent that resection of the tumor is possible. The ascending colon is mobilized and its vascular pedicle preserved. The gut is transected at the cecum and the transverse colon. The cecum then is passed superiorly, by way of the antethoracic, retrosternal, or posterior mediastinal route, and anastomosis to the pharynx and stomach is done. Anastomosis of the transverse colon to the ileum is done, and a pyloroplasty is performed if the vagus nerves have been transected (Fig. 21-7).

The advantages of this technique are that it is completed in one stage; the colon is available in sufficient length so that no tension on the anastomosis should ex-

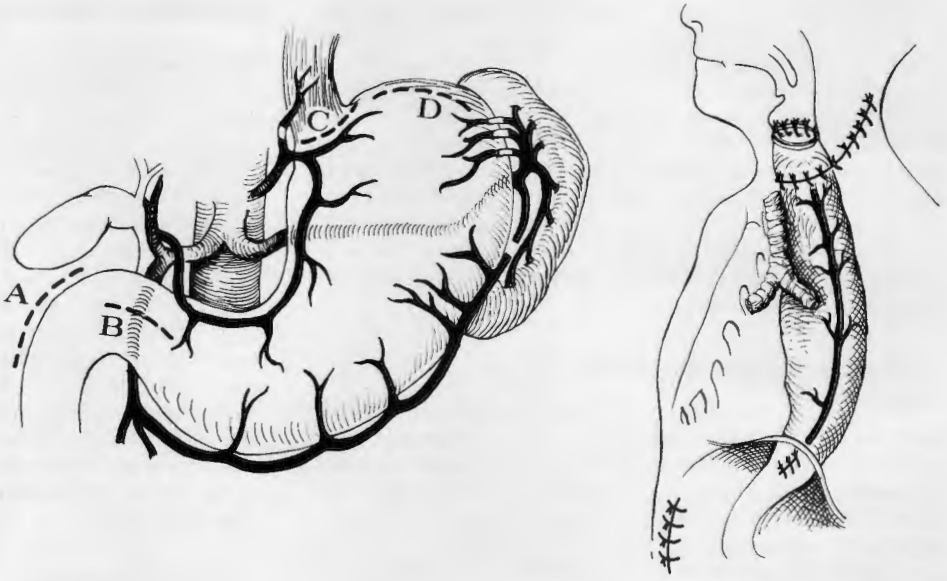

Figure 21-6. Gastric transposition. A, mobilization; B, pyloroplasty; C, transection at esophagogastric junction; D, anastomosis to pharynx.

ist; the caliber of the colon is sufficient for adequate swallowing; the colon is able to withstand regurgitation of the gastric juices; and the stomach is retained in its normal position.[11]

The disadvantages of this operation are that the blood supply of the graft is less dependable than that of the stomach; due to multiple anastomoses, an anastomotic leak may occur, resulting in fatal peritonitis or mediastinitis; the graft has a tendency to dilate; the chances of infection are higher than with use of the stomach; the grafted colon is a passive conduit[11,12]; the bowel may not tolerate postoperative radiation therapy well[7]; the entire esophagus is not always resected[38]; and the postoperative mortality is about 20%.

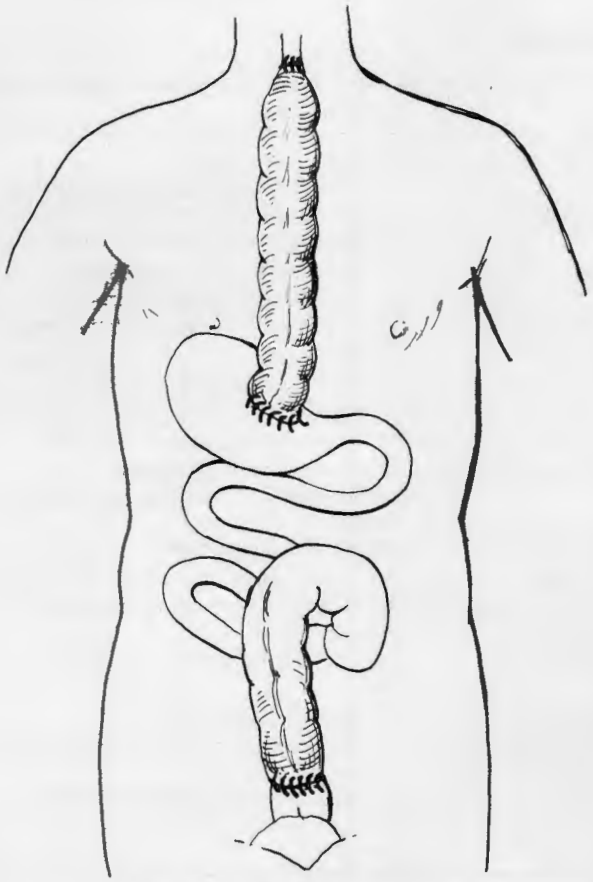

Figure 21-7. Colon interposition.

CHOICE OF LOCATION OF GUT GRAFT. The location of gut graft will be antethoracic, retrosternal, or posterior mediastinal. The advantages and disadvantages of each of these routes are discussed below.

Antethoracic. The major advantage of the antethoracic route is that it is the safest location available. It is not necessary to enter the thorax, and a breakdown in anastomosis is readily accessible and should not result in mediastinitis.[11,20] Disadvantages are that it is longer, it results in a bulge on the chest wall, food must be milked through the graft, and the blood supply may be impaired by angulation over the costal margin.[12]

Retrosternal. The advantages of the retrosternal procedure are that it is cosmetically more appealing than the antethoracic route, it is more convenient to anastomose inferiorly, and incision of the pleura is not required.[11,12] The disadvantages of this location are that the bowel still emerges somewhat anteriorly, and the blood supply may be impeded as the gut passes out of the thoracic inlet (which may require resection of the manubrium and medial clavicles).[11,12]

Posterior Mediastinal. The advantages of the posterior mediastinal route are that it is the shortest route, it allows resection of the entire esophagus, and the vascular pedicle is more easily advanced.[12] The disadvantages are that sometimes it requires thoracotomy, and is associated with the highest mortality and morbidity.[12] However, since the advent of the blunt esophagectomy without thoracotomy, the posterior mediastinal route may be employed with a much lower risk of postoperative complications.

SUMMARY. The various methods of reconstruction, as well as their applications, advantages, and disadvantages, are depicted in Table 21-1.[6,11,18,20,74] The technique of choice for lesions of the cervical esophagus is gastric transposition[28,39,57] or jejunal interposition.[31,32,45,56,65] Gastric transposition has been the reconstructive technique most often employed at our institution. Patients of borderline operability, in whom an intraabdominal procedure is contraindicated, may have reconstruction with a myocutaneous flap.[79] This form of reconstruction is clearly suboptimal compared with gastric transposition or jejunal interposition.

Palliative Surgical Procedures

The goal of palliation is to allow patients to swallow their secretions and enough liquids to maintain adequate nutrition. Palliative surgical procedures are not indicated until a course of palliative irradiation has failed. Surgical procedures include placement of a bypass graft, gastrostomy, or pyriformostomy. A bypass graft generally is achieved by leaving the esophagus in situ and performing a gastric transposition; it provides much better palliation, but at a higher risk of morbidity and mortality than gastrostomy or pyriformostomy. The use of Celestin stents in lesions of the cervical esophagus is rarely successful for obtaining meaningful palliation.[12] Recently, the laser has been used to locally palliate obstructing esophageal cancer. However, laser debulking is associated with the risk of esophageal perforation and mediastinitis.

Radiation Therapy

Radiation therapy has been used in carcinoma of the cervical esophagus since the 1920s with results similar to those of surgery.[41] The introduction of megavoltage equipment in the 1950s allowed higher doses to be given with fewer complications and with a modest improvement in treatment results.[59,60] Treatment planning for carcinoma of the upper esophagus represents one of the greatest technical challenges to the radiation therapist. The esophagus lies only 2 to 3 cm anterior to the spinal cord. Treatment planning includes the lower neck and upper thorax, which have dissimilar shapes and thicknesses, and the esophagus does not pursue a constant course in relation to the skin surfaces. In addition, the lymph nodes at risk must be incorporated into the irregular treatment volume. A feeding jejunostomy may be placed before treatment in patients with poor nutritional status to improve tolerance to a course of high-dose irradiation.

Field Arrangement

Parallel-opposed lateral portals are suitable for a small lesion high in the cervical esophagus, but since most lesions are advanced, it is necessary to use some other arrangement because of the long diameter through the shoulders.

A four-field box technique has been adopted at the University of Florida that consists of an anterior, a posterior, and parallel-opposed lateral portals[49] (Fig. 21-8).

TABLE 21-1. Reconstructive Procedures After Resection for Cancer of the Esophagus

Procedure	Application	Advantages	Disadvantages
Bakamjian deltopectoral flap[6]	Lesions of the cervical esophagus	(1) Low operative mortality	(1) Flap is nonperistaltic (2) Total esophagectomy not performed (3) Multistage reconstruction (4) Stenosis and fistulae are common
Pectoralis major flap[18,56,74,79]	Lesions of the cervical esophagus	(1) Low operative mortality (2) One-stage procedure (3) Improved flap viability	(1) Flap is bulky and nonperistaltic (2) Stenosis and fistulae are common (3) Total esophagectomy not performed
Latissimus dorsi myocutaneous island flap[79]	Lesions of the cervical esophagus	(1) Low operative mortality (2) Single-stage procedure	(1) Total esophagectomy not performed (2) Flap is nonperistaltic
Free jejunal graft[31,32,45,56,65]	Lesions of the cervical esophagus	(1) One-stage procedure (2) Peristaltic graft (3) Same caliber as esophogus	(1) Total esophagectomy not performed (2) Relatively high incidence of graft necrosis or anastomotic leak (3) May not tolerote postoperative irradiation (4) Multiple anastomoses
Gastric transposition[28,39,57]	All esophageal lesions	(1)Total esophagectomy (2) Anastomosis in the neck (3) Good blood supply (4) One-stage procedure	(1) Gastric reflux (2) Graft may not tolerate postoperative irradiation (3) Stomach is no longer in normal location
Colon interposition[11,20]	All esophageal lesions	(1) Good function (2) Stomach in normal position (3) Total esophagectomy may be performed	(1) Multiple anastomoses (2) Blood supply less dependable than for stomach (3) Relatively high operative mortality (4) Graft may not tolerate postoperative irradiation

(Adapted from Mendenhall WM, Million RR. Esophageal cancer. In: Dobelbower RR, ed. Gastrointestinal cancer: radiation therapy, Berlin, Springer-Verlag, 1990:83)

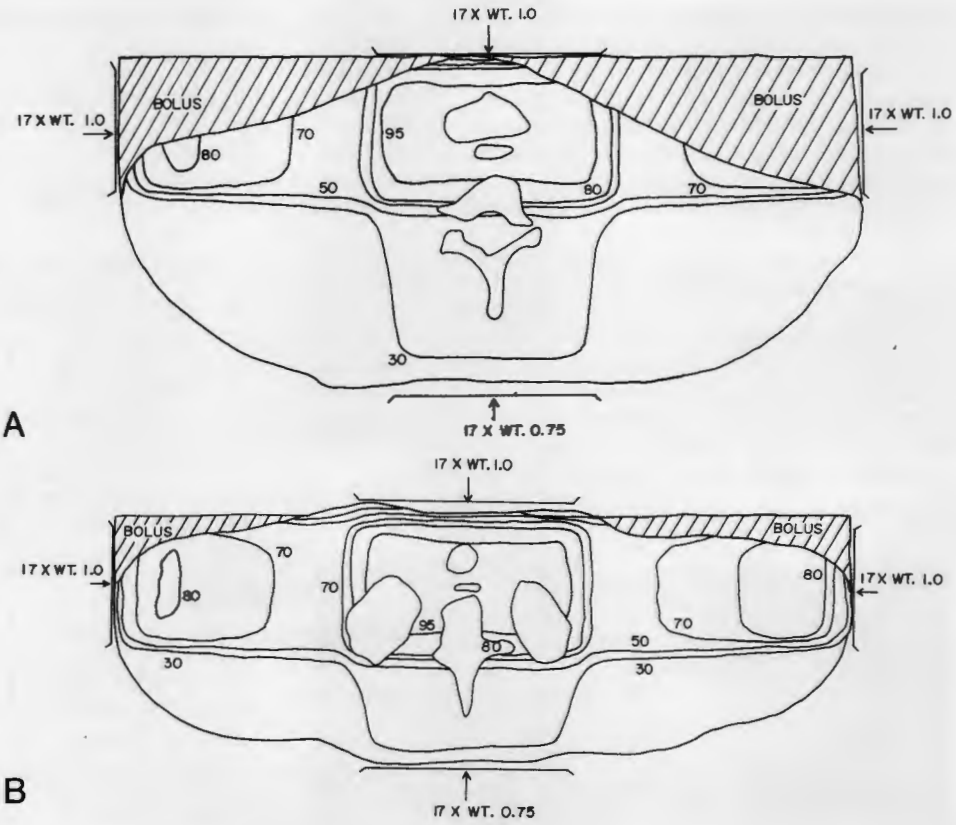

Figure 21-8. Isodose curves for four-field box technique using 17-MV x-ray beam. (*A*) Section at level of C6 vertebra. (*B*) Section at level of T2 vertebra. (Mendenhall WM, Million RR, Bova FJ. Carcinoma of the cervical esophagus treated with radiation therapy using a four-field box technique. Int J Radiat Oncol Biol Phys 1982;8:1437. Copyright © 1982, Pergamon Press, Ltd.)

Beeswax is used to fill the gap above the shoulder; thus, it serves as a compensator[49] (Fig. 21-9). The advantages of this arrangement are that the dose to the spinal cord can be accurately calculated; the likelihood of hot or cold spots is minimized; port films may be more easily interpreted because the beams are not angled; the calculation of tumor doses is more precise; the field reductions are relatively simple; and contoured blocks of Lipowitz's metal may be designed so that the neck and mediastinal nodes may be included without a major increase in treatment volume. The disadvantage of this technique is that one must treat through the shoulders and apex of the

Figure 21-9. Patient in position for treatment of right lateral portal. Note beeswax bolus, blocks made of Lipowitz's metal, and foam body mold. The portal is set up by an isocentric method. The beeswax bolus is placed in position after the portal is aligned. The lateral portal should be checked frequently by imaging films. A strip of neck skin anterior to the thyroid cartilage sometimes can be spared, and is shielded to reduce tangential irradiation of the skin and subcutaneous tissue and to decrease the likelihood of lymphedema. (Mendenhall WM, Million RR, Bova FJ. Carcinoma of the cervical esophagus treated with radiation therapy using a four-field box technique. Int J Radiat Oncol Biol Phys 1982;8:1436. Copyright © 1982, Pergamon Press, Ltd.)

lung so that the availability of high-energy x-rays, although not mandatory, is advantageous. (The lateral dimensions through the shoulder are similar to those through the pelvis, and there is extensive experience with the four-field box technique to irradiate pelvic lesions.) The margin of error on the lateral portals after reduction from the spinal cord is small. This technique requires careful attention to detail, but so does any alternative method.

As an example, a typical course of radiation therapy for a carcinoma of the cervical esophagus would consist of 4500 cGy over 5 weeks using a four-field box technique to include the primary lesion and the regional lymph nodes. The anterior and posterior portals are discontinued, the lateral portals are redesigned to exclude the spinal cord, and the treatment is continued using parallel opposed lateral fields for an additional 2500 to 3000 cGy at 180 to 200 cGy per fraction[49] (Fig. 21-10).

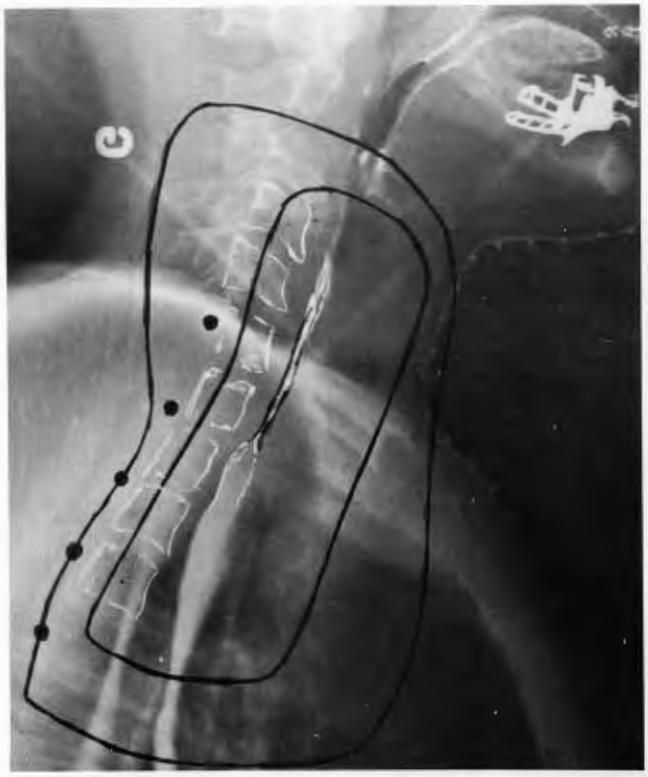

Figure 21-10. Lateral and reduced lateral portals for a cancer of the cervical esophagus located at the inlet. A second and final reduction would just cover the gross lesion. The initial border is generous due to inability to evaluate the mediastinal nodes by palpation. The initial lateral border bows posteriorly on its superior aspect to cover the posterior cervical nodes, and bows anteriorly on its inferior aspect to cover the anterior mediastinal nodes. Note the proximity of the spinal cord to the esophagus. For this patient, it is 2.0 to 2.5 cm from the posterior wall of the esophagus to the anterior portion of the cervical spinal cord, and about 3.0 cm to the thoracic spinal cord. Black dots mark the posterior aspect of the vertebral bodies. Solder wire with lead shot spaced at 1-cm intervals outlines the midline anterior skin surface. (Mendenhall WM, Million RR, Bova FJ. Carcinoma of the cervical esophagus treated with radiation therapy using a four-field box technique. Int J Radiat Oncol Biol Phys 1982;8:1436. Copyright © 1982, Pergamon Press, Ltd.)

Paired anterior wedge fields and the three-field technique (anterior field and two posterior oblique fields) have the disadvantage of requiring complex angles and complex compensators on the oblique fields because the axis of the esophagus is not parallel to the axis of the body. In addition, it is difficult to interpret oblique port films. This is particularly problematic when reducing the size of the fields to avoid the spinal cord.

Lymph Node Treatment

Lymph node chains at risk include the paraesophageal; paratracheal; upper, middle, and lower internal jugular; supraclavicular; spinal accessory; and upper mediastinal. We have observed two patients who developed tumor in the lymph nodes in the upper neck above the irradiation portal. The entire neck on both sides now is included. The upper neck is at special risk when the pyriform sinus or postcricoid area is involved, or when clinically positive lymph nodes are found in the lower neck. The upper neck lymph nodes are treated through a separate anterior, en face portal with a midline shield to reduce mucosal and spinal cord irradiation.

If patients have no clinically apparent adenopathy, the lymph nodes are treated electively with a dose of 4500 to 5000 cGy over 5 weeks.[47] Small positive lymph nodes, 2.0 cm or less in diameter, may be treated by radiation therapy alone.[48] Larger lymph nodes are best managed by a combined approach consisting of radiation therapy directed to the primary tumor and regional lymphatics followed by a neck dissection on the side involved. The conventional radical neck dissection does not resect all of the nodes at risk and should not be relied on as a single mode of treatment.

Simulation

The patient is placed in the supine position with head and thorax in a customized foam mold to maximize setup reproducibility. A bite block or face mask made of polycaprolactone, low-temperature thermal plastic (Aquaplast, WFR Aquaplast Corp., Wyckoff, NJ) may be used to assist in immobilizing the head. Simulation films are obtained with addition of a contrast medium to ascertain the exact location of the lesion, and the anterior aspect of the neck is outlined with wire[49] (see Fig. 21-10). Treatment portals are outlined, and blocks are constructed of Lipowitz's metal. The superior and inferior borders of the field are arranged to make a 5-cm margin on the tumor, the extent of which is defined by barium swallow, indirect laryngoscopy, and esophagoscopy. The superior border may be somewhat more generous in the unlikely event that there are clinically positive lymph nodes in the upper neck. The cervical portion of the spinal cord is included in the initial fields to gain an adequate posterior margin beyond the tumor and to treat the lymph nodes in the neck. The thoracic portion of the spinal cord is included in the field, primarily to gain an adequate margin behind the esophageal lesion. Tattoos are used to mark the anterior source-to-skin distance and the field corners, to ensure reproducibility in the event that the lines are inadvertently removed by the patient. All portals are set up daily from the anterior tattoo, and the treatment technique is isocentric. One cannot rely entirely on ink lines or tattoos to ensure daily reproducibility of the reduced lateral portals. *Imaging films are obtained daily in the lateral fields to ensure accurate treat-*

ment setup, particularly when the field size is reduced to avoid the spinal cord.

Dose

The large size of the initial treatment portals and patients' poor nutritional status predict acute morbidity. Treatment is usually initiated at 180 cGy per fraction. If possible, the daily dose is increased to 200 cGy per fraction once the portals are reduced in size, but only if patients tolerate the treatment and maintain adequate nutrition. The final tumor dose is 7000 to 7500 cGy over 8 to 9 weeks. Field reductions usually are made at 4500 to 5000 cGy, and again at 6000 and 7000 cGy.

Palliative Radiation Therapy

Patients with esophageal cancer almost always present with dysphagia, so that even if treatment is not expected to be curative, some sort of palliative treatment is indicated. Radiation therapy is the simplest noninvasive treatment, and usually is the initial palliative step. The dose most often selected is 3000 cGy in 10 fractions over 2 weeks.

Combined Irradiation and Surgery

Combined radiation therapy and surgery is sometimes employed for carcinoma of the cervical esophagus.[21,37,52] After surgery, a prolonged period of time may occur before postoperative irradiation can be initiated. When irradiation is given preoperatively, patients are treated with 4500 to 5000 cGy at 180 to 200 cGy per fraction, using anterior and posterior fields, with esophagectomy and gastric transposition 4 to 6 weeks after the completion of radiation therapy. This approach has been used at the University of Florida for the last 2 years with encouraging initial results.

If patients are to be treated postoperatively, a higher total dose (6000 to 7000 cGy at 180 cGy per fraction) is necessary, using the previously described four-field box techniques for the initial 4500 cGy, followed by a reduction and boost with lateral fields to the final tumor dose. The final dose depends on the margins of resection: 6000 to 6500 cGy for negative margins; and 7000 cGy for microscopically positive margins.[2]

Adjuvant Chemotherapy

Carcinoma of the esophagus has been noted to respond, at times impressively, to some of the drugs commonly used for squamous cell carcinoma of the head and neck. No definitive evidence exists, however, indicating that chemotherapy, alone or in combination with other treatment modalities, improves the cure rate of patients with cervical esophageal cancer.[35,66]

Management of Recurrence

Recurrence of tumor after definitive treatment is the rule, rather than the exception, in cancer of the cervical esophagus. Recurrence usually is at the primary site or in the regional lymph nodes, and rarely occurs in distant sites alone. The consideration of radical treatment for recurrence at the primary site usually is out of the question, and palliative procedures, such as those previously described, are indicated. Imaging with CT and MRI may help select those patients who are possible candidates for treatment with curative, rather than palliative, intent (see Chaps. 6 and 18). Ipsilateral recurrence in the lymph nodes of the neck, a rare occurrence, could be treated by a radical neck dissection with some hope of salvage.

Summary

Surgery and irradiation yield equivalent results for patients with carcinoma of the cervical esophagus. The advantage of radiation therapy is the lower rates of acute morbidity and mortality in comparison with surgery. The advantage of surgery is that the transposed stomach functions better over the long term than an irradiated esophagus, which tends to become stenotic over time. The philosophy at the University of Florida is to treat patients with resectable cancers who are in good general medical condition with preoperative irradiation and surgery to improve the likelihood of local control and obtain a good functional result. Patients with relatively early lesions who are not good surgical candidates are managed with high-dose radiation therapy. Patients with advanced local disease, and those with distant metastases, are treated with palliative irradiation. Adjuvant chemotherapy is not employed outside of a study setting.

RESULTS OF TREATMENT

The interpretation of treatment results in cancer of the cervical esophagus is hampered by several factors: the rarity of the disease; the tendency to lump results with those of other sites such as the hypopharynx or the remainder of the esophagus; the failure to stage the lesions; the tendency to report primarily on treatment technique in patients with inadequate follow-up (less than 2 years); and the selection bias in favor of surgery in some institutions. Additionally, most authors report only survival rates and ignore the control rate of local and regional disease. Because no randomized trials exist comparing various treatment modalities for carcinoma of the cervical esophagus, treatment decisions must be made based on nonrandomized studies. Treatment results are presented from series of patients treated by surgery, by radiation therapy, and by a combination of the two in Tables 21-2,[24,33,58,61] 21-3,[23,50,58] and 21-4, respectively.[1,12,21,37,54] A cure rate of 10% to 20% with adequate follow-up is consistent with most reported series, regardless of whether patients are treated surgically, with irradiation, or with a combination of modalities.

Local control as a function of T stage and sex is shown in Table 21-5 for a series of patients treated with radical irradiation alone at the University of Florida. Lesions were staged according to the 1983 AJCC staging system.[4] Rates of local control decreased with increasing T stage and were better for women than men. Three patients underwent salvage surgery for a local recurrence, and one was successfully salvaged. Local control for T2 lesions was better for doses of 7000 cGy or more. There was no relationship between local control and dose per fraction over the range of doses used. No T3 lesion was locally controlled at a dose less than 6800 cGy or at a dose per fraction less than 180 cGy. Absolute and cause-spe-

TABLE 21-2. Results of Surgery

Series	Minimum Follow-Up (Y)	Patients Treated	Operative Mortality	3-Y Survival	5-Y Survival
*Mayo Clinic[24]	5	17	4/17 (24%)	No data	2/17 (12%)†
*Tokyo[33]	<1	64	7/64 (11%)	No data	27%‡
Padua[61]	<1	74	14/74 (19%)	15%§	No data
Edinburgh[58]	5	25	No data	No data	4/25 (16%)

* Selected patients received adjuvant radiotherapy.
† Postoperative deaths included.
‡ No. of patients at risk not stated.
§ Actuarial survival.
(Adapted from Mendenhall WM, Million RR. Esophageal cancer. In: Dobelbower RR, ed: Gastrointestinal cancer: radiation therapy. Berlin, Springer-Verlag, 1990:89)

TABLE 21-3. Results of Radical Irradiation Alone

Series	Patients	Minimum Follow-Up (Y)	Local Control	5-Y Survival
University of Florida[50]	34	2	8/31 (26%)*	4/28 (14%)
China[23]	31	5	No data	10/31 (32%)
Edinburgh[58]	76	5	No data	19/76 (25%)

* Excludes three patients who died within 2 y of treatment with the primary site continuously disease-free.
(Adapted from Mendenhall WM, Million RR. Esophageal cancer. In: Dobelbower RR, ed. Gastrointestinal cancer: radiation therapy. Berlin, Springer-Verlag, 1990:90)

TABLE 21-4. Results of Combined Surgery and Radiation Therapy

Study	Patients	Technique	Results
Burdette and Jesse[12] M. D. Anderson Hospital	3	Surgery plus postoperative irradiation	1/3 alive ot 29 mo
Negus*[54] London	5	Surgery plus postoperative irradiation	2/5 alive at 1 y
Goodner[21] Sloan-Kettering Institute	28	Surgery and irradiation (pre- and postoperative)	4/28 alive at >5 y
Lederman[37] London	24	Preoperative irradiation plus surgery	1/24 alive at 5 y
Adams and Smedal[1] Lahey Clinic	2	6000 cGy/35 d (supervoltage) plus resection	1/2 alive at 8 mo

* Selected series.

TABLE 21-5. Cervical Esophagus: Local Control With Irradiation (No. Controlled/No. Treated)

T Stage	Excluded*	Local Control			Salvaged/ Attempts	Ultimate Local Control
		Male	Female	Total		
T1	0	0/1	1/1	1/2	No data	1/2
T2	1	2/7	2/5	4/12	0/1	4/12
T3	2	1/11	2/6	3/17	1/2	4/17
Total	3	3/19	5/12	8/31	1/3	9/13

* Died within 2 y of treatment with primary site continuously disease-free.
Note: University of Florida data.
(Mendenhall WM, Parsons JT, Vogel SB, Cassisi NJ, Million RR. Carcinoma of the cervical esophagus treated with radiation therapy. Laryngoscope 1988;98:770)

TABLE 21-6. Survival After Irradiation (No. Alive/No. Treated)

	Absolute		Cause-Specific	
AJCC Stage	2 Y	5 Y	2 Y	5 Y
I	2/2	0/1	2/2	No data
II	4/13 (31%)	1/11 (9%)	4/12 (33%)	1/9
III	5/19 (26%)	3/16 (19%)	5/18 (28%)	3/15 (20%)
Total	11/34 (32%)	4/28 (14%)	11/32 (34%)	4/24 (17%)

AJCC, American Joint Committee on Cancer.
Note: University of Florida data.
(Mendenhall WM, Parsons JT, Vogel SB, Cassisi NJ, Million RR. Carcinoma of the cervical esophagus treated with radiation therapy. Laryngoscope 1988;98:771)

cific survival rates at 2 and 5 years are depicted by 1983 AJCC stage in Table 21-6.[4]

FOLLOW-UP POLICY

The purpose of follow-up after treatment for cancer of the cervical esophagus is primarily to deal with treatment complications and to detect second primary cancers in the head and neck area; the chance of salvage of radiation therapy or surgical failures is remote, except for very early lesions. Follow-up examination includes periodic esophagogram, CT or MRI, or a combination thereof, especially for those patients in whom salvage treatment is a possibility. Obstructive symptoms after radiation therapy may be due to tumor or fibrosis. Serial studies help differentiate the two. MRI is preferable in patients who are cooperative for reasons discussed previously. Esophagoscopy may be required to distinguish the cause. Careful dilatation may improve a stricture.

COMPLICATIONS OF TREATMENT

Surgery

The complications of surgery depend on the extent of the resection, the method of reconstruction, the general medical condition of patients, and the experience of the surgeon. In general, the operative mortality has declined over recent years. The incidence of postoperative complications for a series of 82 patients undergoing resection and reconstruction for pharyngoesophageal cancers between 1972 and 1982 is shown in Table 21-7.

Radiation Therapy

Acute

The major acute side effect of radiation therapy is radiation esophagitis, which usually appears after 2 weeks of treatment, then plateaus or improves slightly during therapy, and finally resolves 3 to 4 weeks after the completion of treatment. It may be managed symptomatically with acetaminophen (Tylenol, McNeil Products, Ft. Washington, PA) elixir or Aspergum (Plough, Memphis, TN). Split-course irradiation results in decreased severity of esophagitis, but also has been shown to result in a lower cure rate in other head and neck cancers, and is used only if necessary.

With the four-field technique previously described, patients notice erythema of the skin, which may progress to dry desquamation toward the end of treatment. Patches of moist desquamation are unusual.

Moderate xerostomia and loss of taste are noted in patients whose upper neck is irradiated. Taste generally begins to improve 1 to 2 months after treatment is completed, and eventually reverts to near normal. Perma-

TABLE 21-7. Postoperative Complications

Reconstruction	Patients*	Postoperative Mortality	Complications		Success Rate of Reconstruction
			Reconstructive†	Operative†	
Wookey repair	31	3 (10%)	18 (58%)	15 (48%)	21 (68%)
Chest flaps					
Tubed deltopectoral	12	2 (17%)	8 (67%)	7 (58%)	6 (50%)
Tubed pectoralis major	17	1 (6%)	11 (65%)	12 (71%)	7 (41%)
Viscera					
Stomach	12	1 (8%)	4 (33%)	6 (50%)	11 (92%)
Colon	10	2 (20%)	7 (70%)	7 (70%)	5 (50%)
Jejunum	2	0	2 (100%)	1 (50%)	1 (50%)

* 82 patients with 84 reconstructive procedures.
† Reconstructive complications were defined as fistulae, stenosis, and flap necrosis; operative complications included, for example, pulmonary and cardiovascular problems.
(Modified from Surkin MI, Lawson W, Biller HF. Analysis of the methods of pharyngoesophageal recontruction. Head Neck Surg 1984;6:955)

nent xerostomia usually is absent or mild with this treatment, since the parotid glands are not irradiated.

A mild radiation pneumonitis may be detected on roentgenogram if the apex of the lung is included in the treatment volume. However, the apex is relatively resistant to developing symptomatic radiation pneumonitis. The course usually is self-limited and rarely requires treatment. Patients may notice a mild, dry cough 2 to 3 months after completion of treatment. The most serious acute treatment complication occurs when the tumor has invaded the trachea or a major blood vessel and, as the tumor regresses, a fistula occurs. This results in aspiration or hemorrhage, either of which may be fatal. If this complication is anticipated, slow fractionation and split-course irradiation may help to avoid the catastrophe. Tracheoesophageal fistula can occur if the tumor invades through the tracheal wall.

Late

One of the late sequelae of radiation therapy is fibrosis, which may occur in any tissue included in the irradiated volume, specifically the skin, lung, and esophagus. Fibrosis of the lung, when it occurs, fortunately involves the lung apices, which contribute least to pulmonary function, and rarely results in symptoms.

Fibrosis of the esophagus, usually at the site of the tumor, may result in a stricture. Most patients in whom the primary lesion is locally controlled by irradiation develop some degree of narrowing of the involved portion of the esophagus, as seen on roentgenograms. These patients usually must alter their eating habits, but they can maintain adequate nutrition. If a symptomatic stricture develops, a careful bougienage may be performed and may be required periodically. It is imperative that this procedure be performed with caution as perforation may result in fatal mediastinitis.

Another sequela of radiation therapy is Lhermitte's sign, which usually becomes manifest 2 to 3 months after treatment, and may last from several weeks to several months. The most severe late complication of radiation therapy is radiation myelitis, which is rare if the dose to the spinal cord is limited to 5000 cGy at 180 to 200 cGy per fraction. Hypothyroidism may occur because the entire gland is irradiated.

Four of 34 patients (12%) treated with radiation therapy alone at the University of Florida developed significant late complications.[50] Three patients had significant esophageal strictures; one of three required dilatation. One patient developed tracheoesophageal fistula that necessitated surgical intervention, which was unsuccessful. All four patients who had significant late complications were continuously disease-free at the primary site. Of four patients surviving disease free 5 years after treatment, two had significant late complications.

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22

NASAL VESTIBULE, NASAL CAVITY, AND PARANASAL SINUSES

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Primary tumors arising in the nasal cavity and paranasal sinuses usually are considered together. Except in the nasal cavity, where occasional lesions present early because of nasal obstruction, most lesions are advanced at presentation, and the exact site of origin may be uncertain. Primary lesions of the lower half of the maxillary sinus usually can be identified as such.

For treatment planning, cancer of the nasal vestibule generally is considered separately from nasal tumors that develop above and behind the limen nasi. The nasal vestibule is lined with skin, and the squamous cell carcinomas arising from this site have a natural history characteristic of skin cancer. For end-results reporting, vestibule lesions should be reported separately from lesions arising in the posterior nasal cavity.

Cancer of the nasal cavity or paranasal sinuses is relatively rare, with a yearly incidence estimated at a case for every 100,000 people. This cancer occurs more often in men (2:1) and usually appears after 40 years of age, except for occasional tumors of minor salivary gland origin, lymphoma, or esthesioneuroblastoma that may appear before 20 years of age. Esthesioneuroblastoma has a bimodal age distribution (10 to 20, and 50 to 60 years of age).[19,54,66,68] In one large review of the literature, esthesioneuroblastomas were slightly more common in women.[19]

Nasal cavity and ethmoid sinus adenocarcinomas have been linked to occupations associated with wood dust (carpentry, the furniture industry, and sawmill work), boot making, shoe making, baking, and flour milling.[1–3]

Thorotrast, used in the past as a contrast medium for roentgenographic study of the maxillary sinuses, contains the radioactive metal thorium and is a known etiologic agent in maxillary sinus carcinoma. Workers in nickel refining have at least a 40-fold increased risk of developing squamous cell carcinoma of the nasal cavity.[77]

Primary carcinomas of the sphenoid sinuses are rare. They mimic nasopharyngeal carcinoma and are most often diagnosed only after they extend to the nasopharynx.

Frontal sinus neoplasms are also rare.

ANATOMY

Nasal Vestibule

The nasal vestibule is the entrance to the nasal cavity. It is lined by skin having numerous hair follicles and sebaceous and sweat glands. Each vestibule is a three-sided, pear-shaped cavity 1.5 to 2.0 cm in diameter that is surrounded by the lower lateral (alar) cartilage and septum. The vestibule ends posteriorly at the limen nasi, the junction of the lower and upper lateral cartilages[13] (Figs. 22-1 and 22-2). The medial wall is the mobile columella, formed by the medial wing of the alar cartilage and the caudal portion of the cartilaginous septum. The floor is less than 1 cm in length.

Nasal Cavity and Paranasal Sinuses

Nasal Cavity

The nasal cavity begins at the limen nasi (the transition from skin to mucosa) and ends at the posterior nasal apertures or choanae. The choanae are situated immedi-

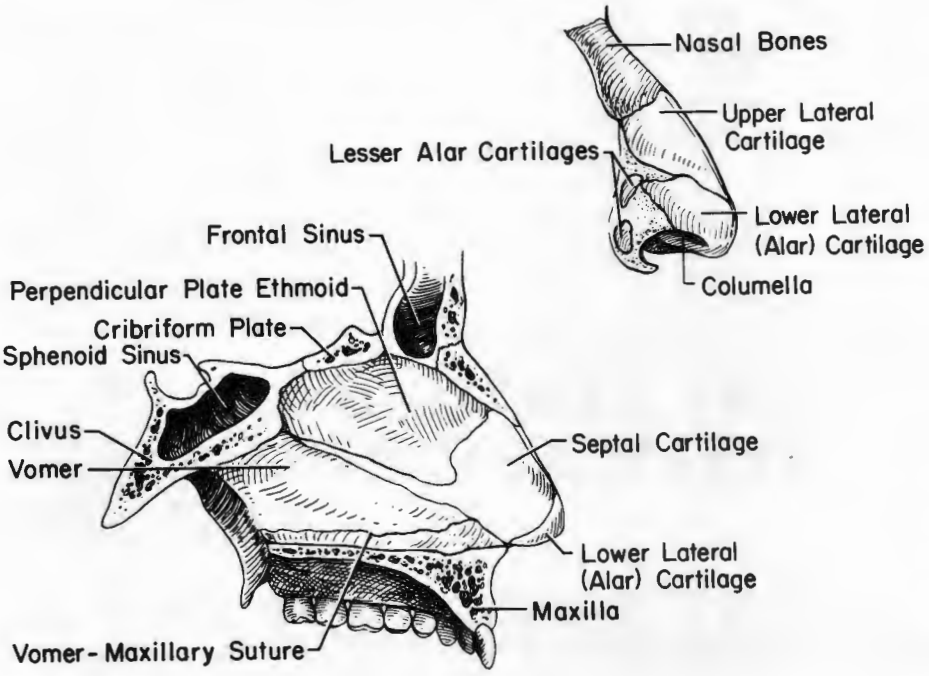


Figure 22-1. Relationship of the bones and cartilages of the nose. (Million RR, Cassisi NJ. Cancer in the head and neck. In: DeVita VT Jr, Hellman S, Rosenberg SA, eds: Cancer: principles and practice of oncology, ed 2. Philadelphia, JB Lippincott, 1985:478)

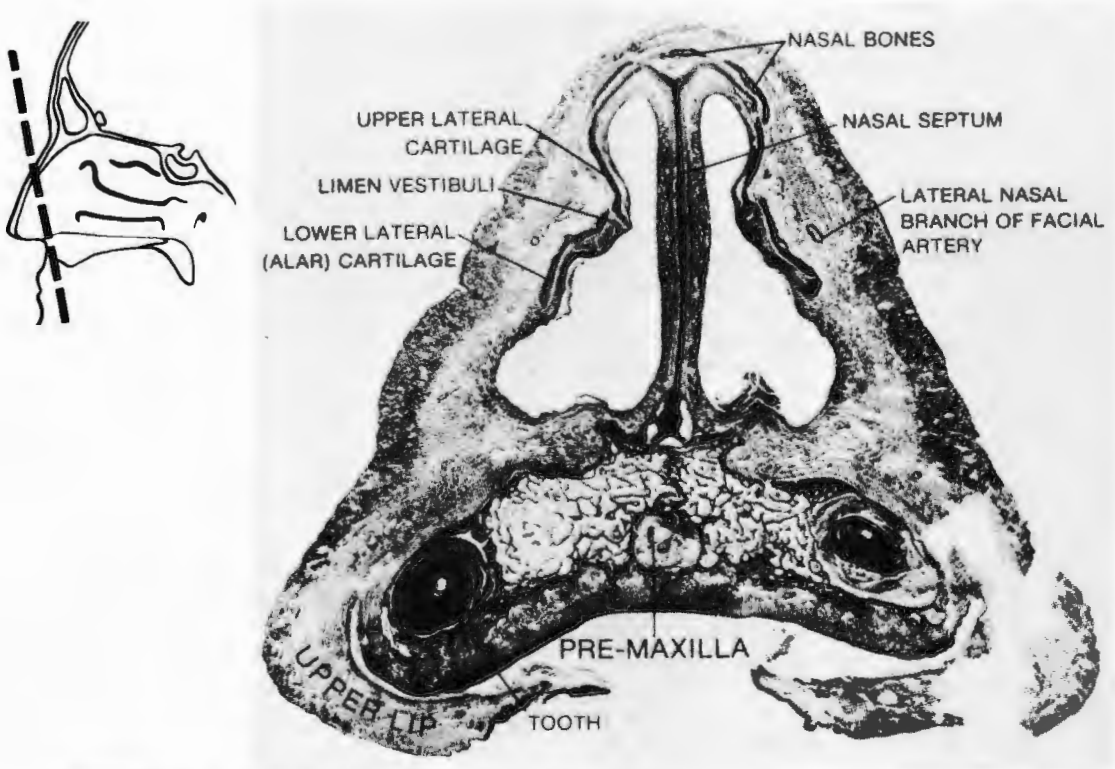


Figure 22-2. Coronal whole-organ section through the vestibule. The upper lateral alar cartilages fuse with the cartilaginous septum. The nasal bones overlap the upper and lower lateral cartilages. The limen vestibuli is the junction of the upper and lower lateral cartilages. (Bridger MWM, van Nostrand AWP. The nose and paranasal sinuses: applied surgical anatomy—a histologic study of whole organ sections in three planes. J Otolaryngol 1978;7[Suppl 6]:4)

ately above the posterior border of the hard palate. They are framed laterally by the medial pterygoid plates and superiorly by the base of skull. The posterior choanae communicate directly with the nasopharynx; each aperture is about 2.5 cm high and 1.25 cm wide. The nasal cavity extends from the hard palate inferiorly to the base of the skull superiorly, and is divided into right and left halves by a midline septum. The composition of the midline septum and the bones and cartilages that compose the roof and sides of the external nose are shown in Figure 22-1.[13] The vomer extends from the undersurface of the body of the sphenoid and forms the lower and posterior part of the septum. The perpendicular plate of the ethmoid forms the upper and anterior part of the septum and is continuous above with the cribriform plate; it is paper thin and offers no real barrier to tumor spread. The septum is often deflected to one side, with the deflection most often occurring along the line joining the vomer with the perpendicular plate of the ethmoid. The septal cartilage forms the majority of the anterior portion of the nasal septum.

Whole-organ sections of the nasal cavity and adjacent sinuses are shown in Figures 22-3 through 22-6.[13] Each lateral wall is composed of thin bony folds that project into the nasal cavity. These are the inferior, middle, and superior nasal concha (turbinates). Each turbinate forms the roof of a passage or meatus that communicates freely with the nasal cavity. The nasolacrimal duct enters the

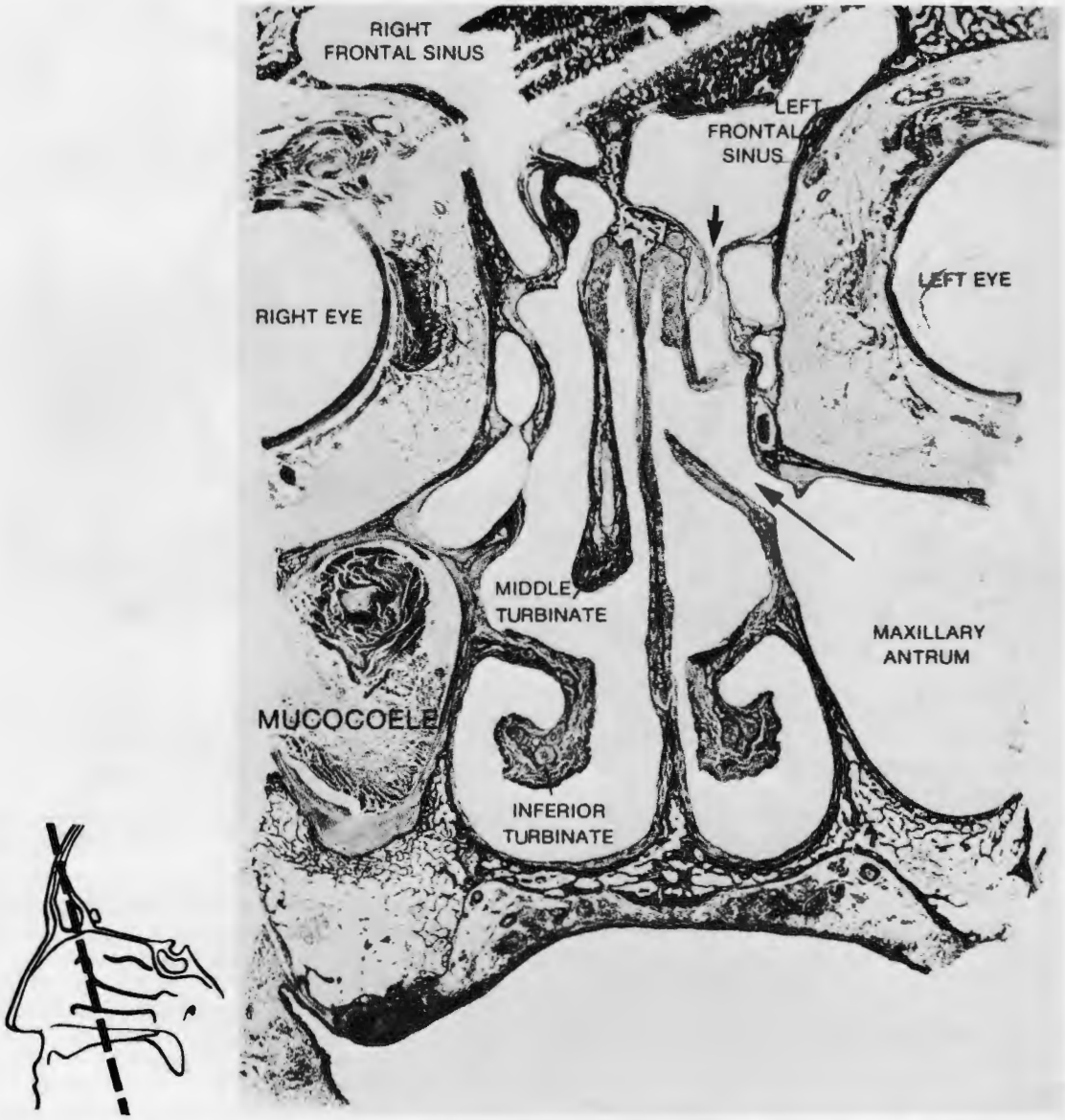


Figure 22-3. Coronal section through frontal sinuses, midnose, and anterior ethmoids. Note left frontonasal duct and ostium of the left maxillary antrum, which open into the middle meatus. The middle turbinate appears to arise from the roof of the nasal cavity near the septum, which is the appearance during physical examination. (Bridger MWM, van Nostrand AWP. The nose and paranasal sinuses: applied surgical anatomy—a histologic study of whole organ sections in three planes. J Otolaryngol 1978;7[Suppl 6]:8)

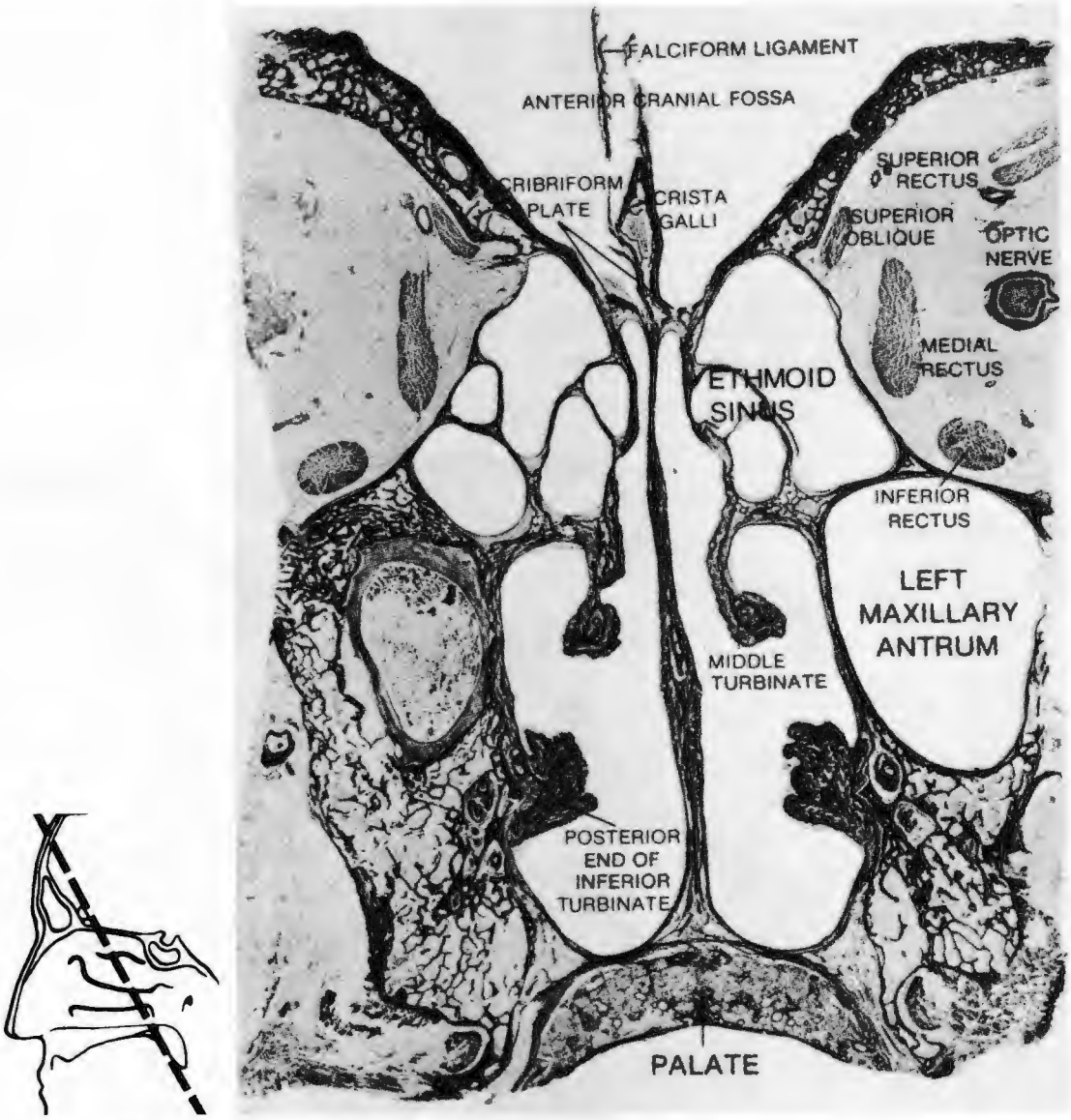


Figure 22-4. Coronal section through the cribriform plate, middle ethmoid sinuses, and posterior inferior turbinates. Note the thinness of the wall separating sinuses from the orbits and nasal cavity. The right and left ethmoid sinuses are completely separated at all levels by the septum and by the narrow superior extensions of the nasal cavities. The ethmoid cells may extend laterally above the orbits. (Bridger MWM, van Nostrand AWP. The nose and paranasal sinuses: applied surgical anatomy—a histologic study of whole organ sections in three planes. J Otolaryngol 1978;7[Suppl 6]:10)

nasal cavity via the inferior meatus. The frontal sinus and anterior and middle ethmoid air cells connect to the nasal cavity via the middle meatus. The superior meatus is short and shallow. It receives the opening of the posterior ethmoid air cells. Immediately behind the superior meatus, the sphenopalatine foramen (which opens into the pterygopalatine fossa) pierces the lateral wall of the nasal cavity. The pterygopalatine fossa lies just inferior to the inferior orbital fissure, and the infraorbital nerve lies just superior to the fossa as it enters the foramen rotundum. The inferior orbital fissure is immediately contiguous with the superior orbital fissure and middle cranial fossa. The sphenoid sinus opens into the nasal cavity through an opening in the anterior wall of the sinus (see Chap. 23, Fig. 23-7).

The olfactory nerves enter the nasal cavity through its roof (the cribriform plate of the ethmoid bone) and distribute nerve fibers over the upper one third of the septum and superior nasal turbinate. The cribriform plate is slightly lower than the roof of the ethmoid sinuses; the external landmark for the cribriform plate is the medial canthal ligament. About 20 branches of the olfactory nerve penetrate the cribriform plate, and these perforations provide an avenue of tumor spread to the floor of the anterior cranial fossa[13] (see Fig. 22-4). In addition to the numerous small foramina for the transmission of the olfactory nerves, the roof presents a separate foramen, situated anteriorly, for passage of the anterior ethmoid nerves and vessels. More posteriorly, the foramen for the posterior ethmoid artery typically lies 5 to 7 mm from

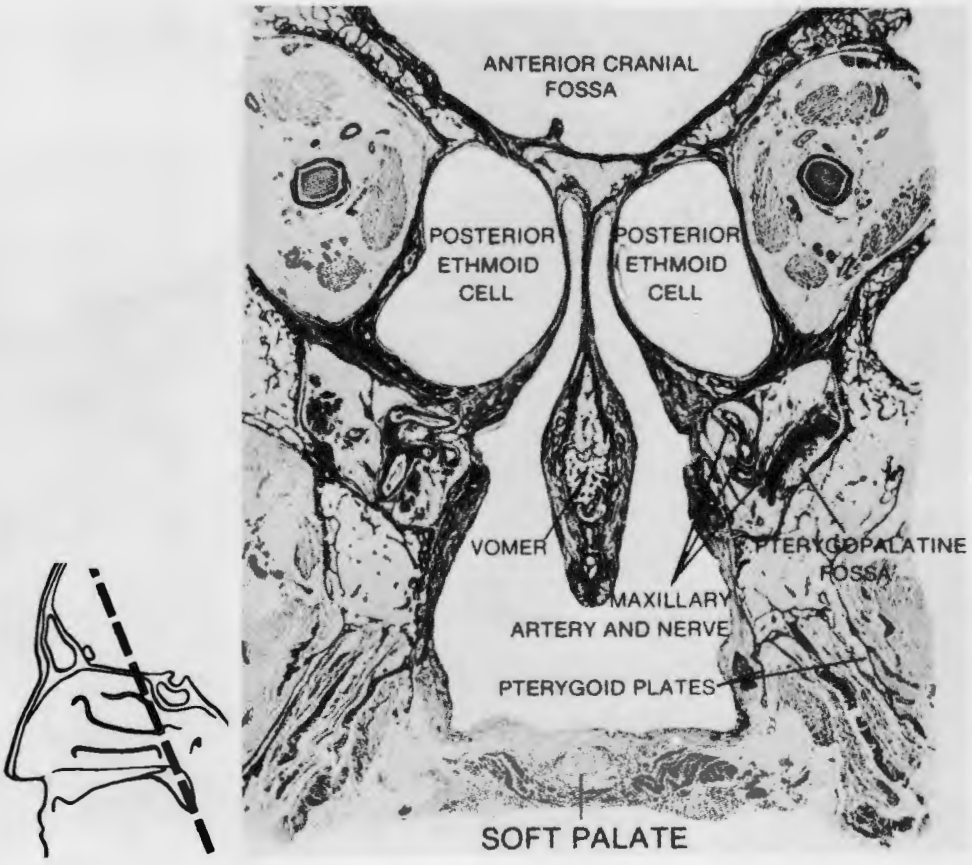


Figure 22-5. Coronal section just behind the maxillary antrum and just anterior to the sphenoid sinus and nasopharynx. Note relationships in the pterygopalatine fossa. (Bridger MWM, van Nostrand AWP. The nose and paranasal sinuses: applied surgical anatomy—a histologic study of whole organ sections in three planes. J Otolaryngol 1978;7[Suppl 6]:12)

the optic canal. The olfactory region of the nasal cavity is limited to the superior nasal concha, the opposed (upper 10 mm) part of the septum, and the intervening roof. The respiratory region comprises the rest of the cavity. The olfactory epithelium is tall, pseudostratified, and columnar with highly specialized cilia. The respiratory epithelium is ciliated columnar. Numerous collections of lymphoid tissue and mucous glands exist beneath the epithelium.

Ethmoid Sinuses

The ethmoid sinuses consist of a labyrinth of air cells lying between the medial walls of the orbits and the lateral wall of the nasal cavity[13] (see Figs. 22-3 through 22-6). The number of air cells varies in number and size from three large to 18 small sinuses on each side. On each side they are arranged into three groups: anterior, middle, and posterior; the three groups are distinguished from each other only on the basis of their sites of communication with the nasal cavity. The partitions between the cavities are thin, and offer almost no resistance to tumor spread. The sinuses are separated from the orbits by the lamina papyracea, a thin, incomplete porous bone that is also easily penetrated by tumor. The middle ethmoid air cells bulge into the lateral wall of the nasal cavity, producing a rounded elevation on the wall of the nasal cavity called the bulla ethmoidalis; the middle ethmoid air cells open anterior and slightly inferior to the bulla via the ethmoid infundibulum and hiatus semilunaris into the middle meatus. The posterior ethmoids are closely related to the optic canal and optic nerve; the posterior ethmoid artery typically is 5 to 7 mm from the canal. The ethmoid air cells extend far anteriorly, and for this reason, anterior ethmoid lesions may present as a subcutaneous mass just in front of the inner canthus[13] (see Fig. 22-6). The anterior cells are covered laterally by the lacrimal bone. The right and left ethmoid cells are anatomically separated by the nasal septum (perpendicular plate of the ethmoid) and the narrow cephalad extensions of the nasal cavities. The roof of the ethmoid sinuses relates to the anterior cranial fossa. The portion of the frontal bone that comprises the roof of the anterosuperior ethmoid air cells is called the fovea ethmoidalis.

Sphenoid Sinus

The sphenoid sinus is a midline structure in the body of the sphenoid bone. The pituitary and optic chiasm lie above, the cavernous sinuses laterally, the nasal cavity and ethmoid sinuses in front, and the nasopharynx beneath. The clivus and brain stem are posterior. Pneumatization varies widely and can extend into all portions of the sphenoid bone. Clival mineralization and fat content also vary considerably. If the sphenoid bone is extensively pneumatized, the sinus may partially surround the optic nerve, carotid artery, and the maxillary and vidian nerves. Although separated by a thin septum, the right and left sides are considered as one in treatment planning; the sides are frequently asymmetrical. The sinus frequently extends into the roots of the pterygoid processes, and when the sinus is exceptionally large, the greater wings of the sphenoid may be pneumatized. Oc-

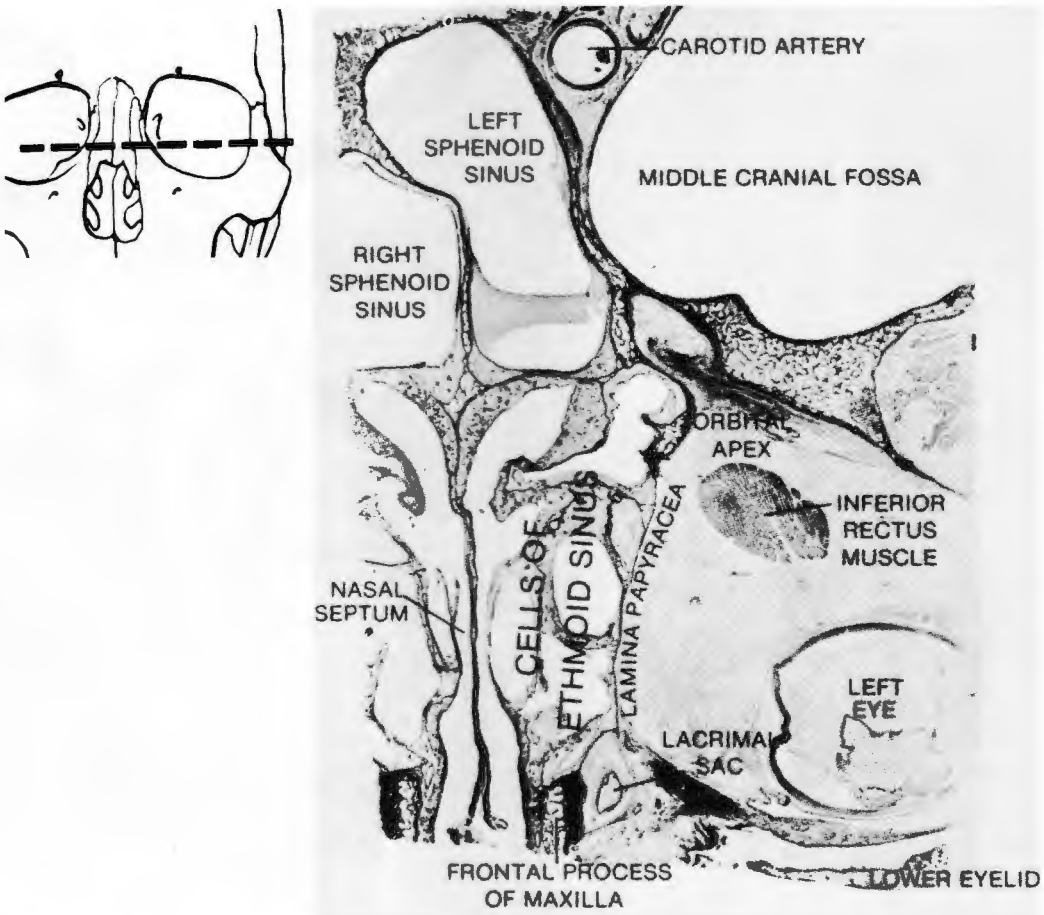


Figure 22-6. Horizontal section through lacrimal sac, orbit, and ethmoid and sphenoid sinuses. The posterior ethmoid cells lie farther laterally than those near the front. The sphenoid sinus is in close relationship to the optic nerve and orbital apex. Note the short distance between the anterior ethmoid sinuses and the inner canthus. (Bridger MWM, van Nostrand AWP. The nose and paranasal sinuses: applied surgical anatomy—a histologic study of whole organ sections in three planes. J Otolaryngol 1978;7[Suppl 6]:26)

casionally, the bony walls have gaps, and the mucous membrane may lie directly against the dura mater. A posterior ethmoid sinus may extend into the body of the sphenoid bone and largely replace a sphenoid sinus. Each sinus connects with the nasal cavity in the sphenoethmoid recess via an aperture in the upper part of its anterior wall (see Chap. 23, Fig. 23-7).

Maxillary Sinus

Whole-organ sections through the maxillary antrum are shown in Figures 22-7 and 22-8.[13] The maxillary sinuses are single pyramidal cavities in the bodies of the maxillae with average measurements of 3.7 cm in vertical height by 2.5 cm in transverse diameter by 3.0 cm anteroposteriorly, and a volume of about 15 cm^3 in adults. Each sinus has four walls: nasal (medial), orbital (roof), facial (anterolateral), and infratemporal (posterolateral). The base of each pyramid is formed by the nasal wall (lateral wall of the nasal cavity); the apex extends into the zygomatic process of the maxilla. The roof or orbital surface of the antrum contains the infraorbital canal. Behind the canine region, the medial surface of the alveolar process aligns with the lateral wall of the nose and the lateral alveolar process aligns with the facial surface of the maxilla, such that the alveolus forms the floor of the antrum. The antral floor is usually about 1.25 cm below the floor of the nasal cavity. The roots of the first and second molar teeth, and occasionally other teeth, often project into the floor of the sinus.

The nasal wall has one or several openings that communicate with the middle meatus under the middle turbinate; an accessory ostium is frequently present[13] (see Fig. 22-3). These openings are nearer the roof than the floor of the sinus. The sinus is drained by mucociliary action. The junction of the orbital and nasal surfaces of the antrum forms the floor of the ethmoid sinus (antroethmoid septum). The posterolateral wall borders the infratemporal fossa and the pterygopalatine fossa. The pterygopalatine fossa lies immediately behind the maxilla and serves as a distribution center of nerves and blood vessels to many areas. Viewed from below, the posterior wall describes a lazy S.

The facial or anterior surface is slightly concave and faces anteriorly and laterally. Most of the surface below the infraorbital foramen is palpable through the gingivobuccal sulcus above the premolar teeth, and the portion above the foramen is easily palpated through the skin.

Before it emerges onto the face, the infraorbital nerve gives off an anterior superior alveolar branch that runs in the facial wall of the maxillary sinus to the incisor and canine teeth.

The posterior superior alveolar nerve arises from the maxillary nerve in the pterygopalatine fossa and runs downward and forward to pierce the infratemporal surface of the maxilla and descend under the mucosa of the maxillary sinus.

Frontal Sinuses

The frontal sinuses are two irregular, usually asymmetrical air cavities separated by a thin, bony septum. The sinuses lie between the outer and inner tables of the frontal bone. They connect to the middle meatus of the nasal cavity by either the frontonasal recess[13] (see Fig. 22-3) or ethmoid infundibulum. Frontal sinus cells may extend far laterally in the orbital process of the frontal bone. They are separated from the anterior ethmoid cells by thin, bony walls. The posterior wall separating the frontal sinus from the anterior cranial fossa is thick in most patients.

Lymphatics

Nasal Vestibule

The lymphatic trunks run mainly to the submandibular nodes. A small risk for involvement of facial nodes exists, especially those just behind the commissure of the lip in the cheek (buccinator node) and those at the crossing of the facial vessels over the mandible (mandibular nodes). Infraorbital and malar nodes are at risk, but no case of metastasis is documented. Metastasis to facial nodes is more likely if disease recurs. Parotid area lymph nodes are rarely involved, but spread to facial nodes may herald an increased risk. The retrozygomatic node may be involved (see Chap. 6, Fig. 6-2).

Nasal Cavity and Paranasal Sinuses

The lymphatics of the nasal cavity are separated into the olfactory group and the respiratory group. According to Rouvière,[63] they do not communicate with each other. The lymphatic network of the olfactory region is connected with the subarachnoid spaces, which allows some

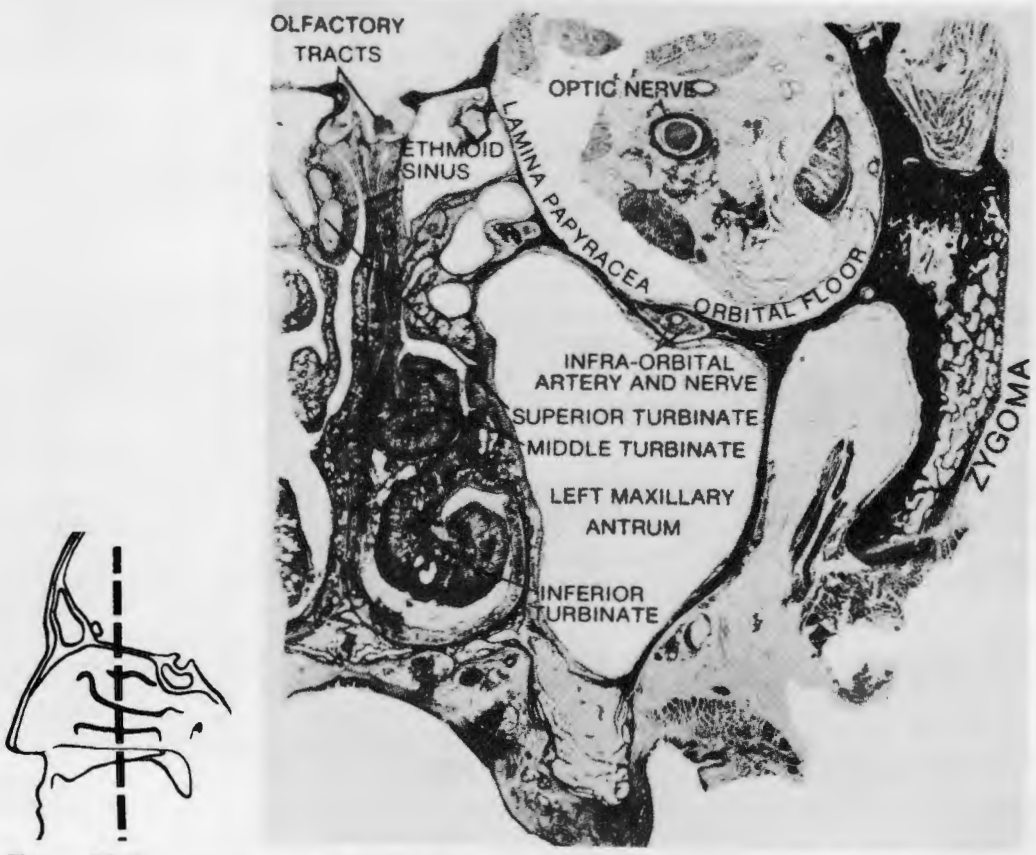


Figure 22-7. Coronal section through the maxillary antrum. Note the thinness of all walls except the hard palate. Lateral to the antrum is the buccinator muscle and fat pad. (Modified from Bridger MWM, van Nostrand AWP. The nose and paranasal sinuses: applied surgical anatomy—a histologic study of whole organ sections in three planes. J Otolaryngol 1978;7[Suppl 6]:14)

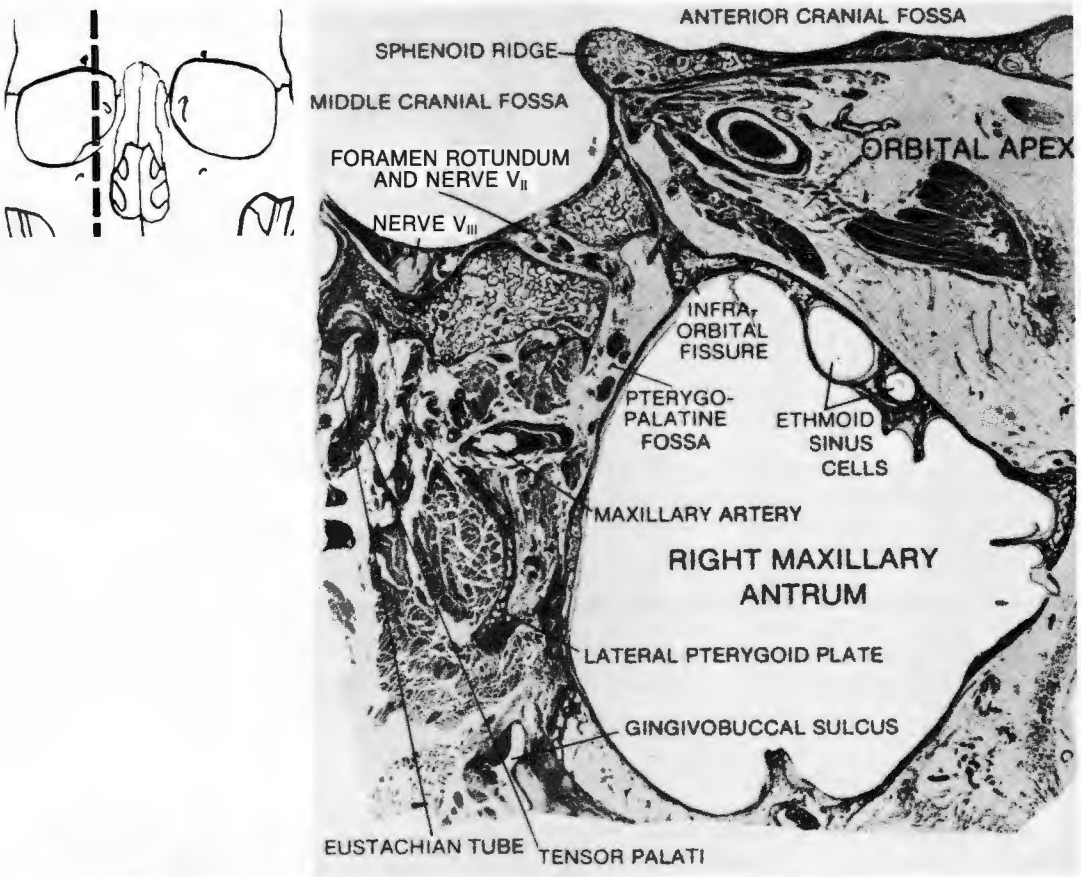


Figure 22-8. Sagittal section through antrum and apex of the orbit. The orbital apex communicates with the pterygopalatine fossa by way of the infraorbital fissure. Extension of the antral tumor through the posterior wall provides access to the middle cranial fossa along the cranial nerves and vascular foramina. (Bridger MWM, van Nostrand AWP. The nose and paranasal sinuses: applied surgical anatomy—a histologic study of whole organ sections in three planes. J Otolaryngol 1978;7[Suppl 6]:18)

absorption of cerebrospinal fluid by the lymphatics.* The lymphatics of the olfactory region of the nasal cavity run posteriorly to terminate in lymph nodes medial to the carotid at the C1–2 level, the retropharyngeal lymph nodes. The lymphatics of the respiratory nasal cavity also run posteriorly to terminate a bit lower, either in a junctional, subdigastric, or submandibular lymph node. The capillary lymphatic plexus of the nasal cavity is well developed over the middle and inferior turbinates, in the olfactory region, and around the choanae, but is sparse over the lower septum.

Rouvière[63] admits that knowledge of the lymphatics of the paranasal sinuses is imperfect. He describes unusually delicate and sparse lymphatics of the frontal, ethmoid, and maxillary sinuses that connect with those of the nasal mucosa, and thus have similar terminations. Metastases from carcinoma of the paranasal sinuses are uncommon, even though lesions are frequently advanced. It is literally unheard of for a patient with a paranasal sinus tumor to present with cervical lymphadenopathy and an asymptomatic primary lesion. Metastases probably only occur once tumor has extended beyond the paranasal sinuses to areas containing an abundant supply of capillary lymphatics, such as the nasopharynx, buccal mucosa, nasal cavity, and skin.

Enlarged lymph nodes associated with acute or chronic sinusitis are uncommon, which indirectly indicates a paucity or absence of capillary lymphatics in the sinuses.

PATHOLOGY

A wide variety of neoplasms, benign and malignant, affect this area.

* The importance of the lymphatic connections with the central nervous system is uncertain. In rabbits and cats, proteins and red blood cells can be partially removed from the cerebrospinal fluid and returned to the blood stream by this route, although most absorption takes place through the arachnoid villi. An injection of Gerota substance into the subarachnoid space of humans near the cribriform plate is transmitted across the plate to the olfactory lymphatics of the nasal cavity. Földi[21] has shown that complete obstruction of the cervical lymphatics in animals leads to a neurologic disorder that he termed *lymphogenic encephalopathy*. This syndrome was characterized by increased intracranial pressure with papilledema, cerebral edema, lymphedema of the head, listlessness, headache, and decreased mental ability.

Nasal Vestibule

The nasal vestibule is covered by skin. Almost all of the vestibule lesions are squamous cell carcinomas; few are basal cell carcinomas or adnexal carcinomas.

Nasal Cavity and Paranasal Sinuses

Benign Tumors

Inflammatory polyps, giant cell reparative granuloma, benign mixed tumors of minor salivary gland origin, benign odontogenic tumors, and necrotizing sialometaplasia are some of the benign lesions appearing in this area.[39]

Malignant Tumors

CARCINOMA. Squamous cell carcinoma, or one of its variants, is the most common neoplasm, and the maxillary antrum is the most commonly involved primary site for this histologic type.

Minor salivary gland tumors account for 10% to 15% of neoplasms in this region. The incidence of the different types of salivary gland tumors in the upper airway differs significantly from the incidence of these carcinomas in the major salivary glands. In a series of 224 glandular neoplasms of the sinonasal tract from the Armed Forces Institute of Pathology (Washington, D.C.), Heffner and coworkers[28] noted that adenocarcinoma was the most common histologic type, representing 47% of such neoplasms, followed by adenoid cystic (30%), benign mixed (18%), and mucoepidermoid carcinoma (5%). Acinic cell carcinomas of the nasal cavity or paranasal sinuses are exceedingly rare.[41] Adenocarcinoma tends to arise in the nasal cavity and ethmoid sinus; adenoid cystic carcinoma, in the maxillary antrum or nasal cavity; and benign mixed tumor, in the nasal cavity. Adenocarcinomas may have a variety of architectural patterns, all of which bear some resemblance to gastrointestinal adenocarcinomas. The papillary form tends to be the best differentiated and the most localized, and is the form most often associated with the carcinomas of wood workers.[10]

The possibility of metastasis from a distant site should always be kept in mind when any adenocarcinoma of the sinonasal tract is encountered; renal cell carcinoma is the most frequent primary lesion.

INVERTED PAPILLOMA. The histologic picture of an inverted papilloma is that of a papilloma growing into rather than out of the stroma. At least 20 different terms have been used to describe these lesions, including schneiderian cell papilloma, cylindrical cell papilloma, fungiform papilloma, and epithelial papilloma. Although usually histologically benign, it is best considered "grade ½" carcinoma because of its frequent (10% to 15%) association with squamous cell carcinoma and its often-aggressive clinical course, even in the absence of frank malignancy. When associated with squamous cell carcinoma, the cancer is present at the time of initial diagnosis and may be low grade or high grade.

LYMPHOMA. Malignant lymphoma, usually histiocytic, occurs in about 5% of cases. It is frequently a locally destructive lesion because it more often arises in bone than in soft tissue (see Chap. 34).

PLASMACYTOMA. This is described in the section on plasmacytoma in Chapter 34.

SARCOMA. A wide range of soft tissue and bone sarcomas are reported to have arisen in the nasal cavity and paranasal sinus region, including chondrosarcoma, osteosarcoma, Ewing's sarcoma, and most of the soft tissue sarcomas (see Chaps. 32 and 33).

ESTHESIONEUROBLASTOMA (OLFACTORY NEUROBLASTOMA). Esthesioneuroblastoma is a malignant tumor that originates from the olfactory nerves and has a histologic picture resembling adrenal neuroblastoma or retinoblastoma. Neurosecretory granules have been identified in ultrastructure examinations. Histologically, in the past it may have been confused with undifferentiated carcinoma, undifferentiated lymphoma, or meningioma; but with modern immunohistochemical techniques, this is no longer a problem. Currently a trend exists to include this tumor with the neuroendocrine carcinomas.

MELANOMA. Malignant melanoma accounts for about 5% to 10% of cancers of the nasal cavity. Melanomas of the paranasal sinuses are rare.[37,62] The lesions have their highest incidence in the fifth through eighth decades, occurring with almost equal frequency in men and women, and in blacks and whites.[10] They may be either heavily pigmented or achromatic (pink). Amelanotic melanomas tend to occur in the region of the olfactory epithelium.

MIDLINE GRANULOMA. Much confusion exists regarding the terms midline granuloma, lethal midline granuloma, nonhealing midline granuloma, polymorphic reticulosis, lymphomatoid granulomatosis, malignant midline reticulosis, Wegener's granulomatosis, and other terms used to describe a group of poorly understood conditions that lead to progressive mid-facial erosion. From a practical standpoint, the critical feature seems to be in distinguishing Wegener's granulomatosis from non-Wegener's, since treatment of the former is with systemic therapy whereas treatment of the latter condition is with localized radiation therapy, unless systemic spread has occurred. Differentiation between polymorphic reticulosis (which frequently manifests angiocentric or angioinfiltrative growth patterns), lethal midline granuloma (which is usually described as a nonspecific and inflammatory destructive process), and localized lymphoma is, in some respects, a moot point from a therapeutic standpoint because radiation therapy is the usual treatment for all three.

Lethal, midline, nonhealing granuloma refers generally to a progressively destructive condition that involves the nose, paranasal sinuses, and hard palate and produces secondary erosion of these and other contiguous structures. Unchecked, the disease is fatal, usually after an extended illness. Death results from extension to the central nervous system, hemorrhage, sepsis, or inanition. The etiology is debated.

PATTERNS OF SPREAD

Nasal Vestibule

Early lesions often present as superficial ulcerations of the membranous septum or columella with physical findings consisting of little more than a crust or scab.

More advanced lesions perforate the membranous or cartilaginous septum or invade the alar cartilage and grow through to the skin surface. The upper lip and columella are frequently invaded. Posterior growth into the nasal cavity occurs late or after recurrence. Advanced lesions grow into the gingivolabial sulcus and may become adherent to or invade the premaxilla. Nasal vestibule carcinomas are deceptive to the novice, since they are often more extensive than one would imagine from the physical findings. This observation is confirmed by the numerous patients seen with positive margins or recurrence after attempted excision.

Metastatic Spread

Lymph node spread is usually to a solitary ipsilateral submandibular node, but may be bilateral. The facial nodes are also at some risk. The facial nodes are subcutaneous lymph nodules (intercalated nodes) located along collecting trunks. Facial nodes are commonly located at either the level of, or above, a line drawn from the lip commissure to the base of the auricle (buccinator nodes) or on the external surface of the mandible in front of the masseter muscle near the crossing of the facial vessels over the midbody of the mandible (mandibular nodes) (see Chap. 6). The buccinator nodes are best detected by bimanual (simultaneous intraoral and extraoral) palpation of the cheek; the mandibular nodes are palpated in the subcutaneous tissues in front of the anterior facial vein. Periparotid, intraparotid, and submental lymph nodes are at low risk of involvement. Lymph node involvement is most likely in patients with extension to the floor of the vestibule, base of the columella, or mucosa of the upper lip, and in patients with recurrent local disease. Inflammatory (reddened) skin changes are a signal of dermal lymphatic involvement and a high risk for lymph node involvement. Lymph node metastases on admission are noted in about 5% of patients[8,40,47,81] and subsequently develop in another 15% of patients when the lymphatic areas have not been electively treated. Distant metastasis as the only site of failure is rare.[81]

Nasal Cavity and Paranasal Sinuses

Nasal Cavity

The routes of spread are essentially the same for the various histologic types, with the exception that minor salivary gland tumors have a greater propensity for perineural spread; such spread most commonly occurs in adenoid cystic carcinoma. Perineural spread may occur with other histologic types, particularly in patients with recurrent tumors.

Perineural spread may be present histopathologically without imaging or clinical findings.

Lesions that arise in the olfactory region invade the ethmoid sinuses, orbit, and anterior cranial fossa. Massive invasion of the frontal lobes of the brain at the time of diagnosis of esthesioneuroblastoma has been observed[69]; in one patient from the University of Florida (Gainesville), personality change was the chief presenting complaint. These lesions also tend to destroy the septum, and may invade through nasal bone to the skin. Lesions arising on the lateral wall of the nasal cavity invade the medial wall of the maxillary sinus, the ethmoid sinuses, the pterygomaxillary fossa, and the orbit.

About half of the patients seen at the University of Florida with cancers of the nasal cavity or ethmoid sinuses had tumor invasion of the orbit, and in about half of those patients the degree of invasion was advanced, leading to blindness, proptosis, or a palpable orbital mass.[56] The nasopharynx and sphenoid sinus are secondarily invaded in advanced nasal cavity cancers. Nasopharyngeal invasion usually occurs by direct mucosal extension through the posterior choana.

Inverted papilloma almost always arises from the lateral nasal wall, although isolated cases arising in the sinuses without nasal cavity involvement have been reported,[52] as have rare cases in which the lesion arose from the nasal septum or in which the tumor was bilateral.[7] True multicentricity is rare.[35] The lesions tend to be firm, polypoid, bulky, and more vascular than inflammatory polyps. The point of attachment to the lateral nasal wall may be small relative to the overall size of the tumor. Extension to adjacent paranasal sinuses is common. Spread to the orbit and anterior skull base is much less frequent than sinus involvement. Much of the so-called sinus involvement often turns out to be secondary obstructive disease. The anatomic distribution of tumor in 32 patients at the time of lateral rhinotomy is shown in Table 22-1. Bone erosion appears to be a result of pressure necrosis rather than direct tumor infiltration. At least one case of lymph node metastasis has been reported.[64]

Ethmoid Sinuses

Lesions of the ethmoid sinuses have many options for local spread owing to their location and the thin, porous bony walls, none of which offers particular resistance. Invasion through the lamina papyracea into the medial orbit is common. The anterior ethmoid cells are covered laterally by the small, thin lacrimal bone and the frontal process of the maxilla[13] (see Fig. 22-6). Thus, the ethmoid air cells extend far anteriorly, within 1 cm of the inner canthus, and the tumor may present as a subcutaneous nodule or involve the inferior frontal sinus.

Extension into the nasal cavity, maxillary antrum, anterior cranial fossa, sphenoid sinus, and nasopharynx all are common. Extension to the middle cranial fossa may occur directly via the orbital apex, or perineurally along the nerves traversing the superior orbital fissure.

TABLE 22-1. Inverted Papilloma: Findings at Lateral Rhinotomy in 32 Patients

Findings at Surgery	No. Patients (%)
Nasal fossa	32 (100%)
Ethmoid sinus	24 (75%)
Antrum	23 (72%)
Frontal sinus	5 (16%)
Lamina papyracea	3 (9%)
Nasopharynx	2 (6%)
Sphenoid sinus	1 (3%)
Orbit	1 (3%)

(Myers EN, Fernau JL, Johnson JT, Tabet JC, Barnes EL. Management of inverted papilloma. Laryngoscope 1990;100:483)

Sphenoid Sinus

Little information exists regarding spread patterns for tumors arising in the sphenoid sinus. It is probable that some lesions diagnosed as advanced nasopharyngeal tumors are, in reality, primary sphenoid sinus lesions that are diagnosed when they erode into the nasopharynx. The fact that some advanced nasopharynx lesions have no neck metastases is suggestive of their origin in the sphenoid sinus, a site with sparse, if any, capillary lymphatics, rather than from the nasopharynx with its copious lymphatics. Some lesions diagnosed as sphenoid sinus cancer are eventually found to be invasive pituitary adenomas, skull-base metastases, malignant round cell tumors (eg, plasmacytoma), or chordomas. Primary squamous cell carcinoma arising in the sphenoid sinus is a rare lesion. More commonly, the sphenoid is involved by direct extension from other sites.

The sphenoid sinus is closely related to the cranial nerves in the cavernous sinus: the third, fourth, sixth, and the ophthalmic and maxillary branches of the trigeminal nerve (see Chap. 23, Fig. 23-10). The sphenoid sinus is closely related to the apex of the orbit and optic nerve, depending on the degree of pneumatization[13] (see Fig. 22-6). These structures are at risk for early tumor invasion. None of four patients seen at the University of Florida had evidence of orbit involvement.

Maxillary Sinus

The pattern of spread and bone destruction largely is dependent on the site of origin within the sinus. Lesions arising in the anterolateral infrastructure tend to invade through the lateral inferior wall and present in the oral cavity when tumor erodes through the maxillary gingiva, or into the gingivobuccal sulcus. When the tumor erupts into the oral cavity, it is at first submucosal, causing elevation of the mucosa, loosening of teeth, or improper seating of a denture. Ulceration follows, with the development of an oral–antral fistula.

Lesions arising on the medial infrastructure readily develop extension to the nasal cavity owing to the thin, porous nature of the medial wall.

Lesions of the posterior infrastructure erode through the posterolateral wall into the infratemporal fossa, or directly posteriorly to the pterygopalatine fossa and pterygoid plates. The groove for the posterior superior alveolar neurovascular bundle is an inherent area of weakness in the posterior antral wall. Tumor in the pterygopalatine fossa commonly leads to involvement of the pterygopalatine (sphenopalatine) ganglion and palatine nerves. Pterygopalatine fossa involvement greatly reduces the likelihood of cure. Cancer in the fossa has access to the following[13,57] (see Fig. 22-8):

1. Middle cranial fossa via the foramen rotundum
2. Foramen lacerum via the pterygoid canal
3. Nasopharynx via the sphenopalatine foramen
4. Infratemporal fossa via the pterygomaxillary fissure
5. Orbital apex via the inferior orbital fissure

Once tumor has spread to the retroantral fat, it may go on to involve the pterygoid muscle and even the temporalis insertion on the coronoid process. Extension of tumor to the orbit occurs directly through the roof of the maxillary sinus, by extending into the ethmoid sinuses, then through the lamina papyracea, or by way of the pterygopalatine fossa and inferior orbital fissure.

Tumors arising in the upper half (suprastructure) of the antrum have two general patterns of spread. One group grows laterally, invades the malar process of the maxilla and the zygomatic bone, and produces a mass just below the lateral floor of the orbit. The soft tissue mass becomes large and eventually ulcerates through to the skin, producing an antrocutaneous fistula. The orbit is invaded laterally, displacing the eye inward and upward. The temporal fossa and zygomatic arch may become involved in advanced lesions.

The suprastructure cancers that develop medially invade the nasal cavity, ethmoid sinuses and frontal sinus, the lacrimal apparatus, and the medial inferior orbit. The antroethmoid septum is easily breached by tumor. It may be impossible to determine whether the site of origin is the maxillary antrum, nasal cavity, or ethmoid sinus. These lesions are sometimes referred to as *crossroads* tumors, because they develop at or near the junctions of the maxillary antrum, nasal cavity, and ethmoid sinuses. Tumors involving the roof of the antrum may develop perineural extensions along the infraorbital nerve, thence through the inferior orbital fissure, across the upper part of the pterygopalatine fossa, and into the middle cranial fossa via the foramen rotundum.

Lymphatics

The incidence of lymphatic metastases on admission is 10% to 15% for nasal cavity, ethmoid sinus, and maxillary antrum tumors. Another 10% to 15% of patients develop lymph node metastases in follow-up. The risk increases if tumor recurs at the primary site. The risk of lymphatic metastases for primary sinus lesions is related to extension of the tumor outside the sinus to areas with capillary lymphatics. Maxillary sinus tumors that invade the oral cavity and involve the buccal mucosa or the maxillary gingiva or hard palate may spread to the submandibular and upper internal jugular nodes. Lesions that invade the nasal cavity or nasopharynx spread posteriorly to the retropharyngeal lymph nodes, and to the upper internal jugular node area. Patients with cancer that invades the skin after growing through the anterior or lateral antral wall are at risk for involvement of the facial nodes including infraorbital, malar, buccinator and mandibular. Parotid nodes are rarely involved.

Esthesioneuroblastoma, minor salivary gland tumors, melanoma, and sarcomas all may demonstrate lymph node metastases.

A case report[64] exists of a garden-variety inverted papilloma, managed by excision, that developed three lymph node metastases 1 year later which showed characteristic inverted papilloma.

Distant Metastasis

Five percent to 15% of patients die of distant metastasis as the sole site of recurrence.[6,19,56] Seeding of the cerebrospinal fluid by esthesioneuroblastoma occasionally is observed.[17,61]

CLINICAL PICTURE

Nasal Vestibule

Lesions of the nasal vestibule present with few symptoms other than a mass growing in the entrance to the nose with crusting, scabbing, and occasional minor

bleeding. Pain, if it occurs, is usually modest, even with destruction of cartilage or involvement of the lip. Secondary infection sometimes is present, resulting in extreme tenderness of the nose and lip. The lesion may be localized to one distinct area of the nasal vestibule, but it frequently fills the nasal vestibule so that the site of origin cannot be determined.

Physical Examination

Erythema or induration of the upper lip may be subtle. The gingivolabial sulcus is inspected and palpated with the index finger. The primary lesion in the vestibule is best visualized by retracting the ala with the wood end of a cotton-tipped applicator, since the nasal speculum itself may get in the way of adequate visualization. Posterior tumor extensions are sought with the fiberoptic telescope. The buccinator and facial nodal region are palpated bimanually with the index finger of one hand sweeping over the buccal mucosa intraorally while the other hand simultaneously palpates the exterior of the cheek. Special attention is directed to bimanual examination of the submandibular lymph nodes.

Nasal Cavity and Paranasal Sinuses

Nasal Cavity

Patients with tumors in the nasal cavity often present with a history of chronic recurrent nasal obstruction and "sinus trouble," which has recently worsened. The symptoms are unilateral, low-grade, chronic infection with discharge, obstruction, and usually minor, intermittent epistaxis. They mimic those associated with nasal polyps, and, since many patients with nasal neoplasms have a prior history of nasal operations for polyps, cancer often is missed in an early stage. Patients often complain of sinus trouble and intermittent anterior headache. Subsequent symptoms depend on the pattern of growth. Lesions arising in the olfactory region may cause expansion of the bridge of the nose, and a submucosal mass may appear near the inner canthus and eventually ulcerate. The mass may protrude from the nose. Obstruction of the nasolacrimal system may cause epiphora and lead to diagnosis of and treatment for dacryocystitis. Extension through the cribriform plate or into the ethmoid sinus is accompanied by frontal headache. Aberration or loss of smell is unusual, but has been noted in one patient as an early symptom. Invasion of the medial orbit produces proptosis and diplopia; a mass may be palpated in the orbit. Indirect examination of the nasopharynx may show early submucosal invasion through the posterior nares.

Inverted papilloma most commonly presents with unilateral nasal obstruction. At least 50% of patients have had prior surgical procedures, most commonly nasal polypectomy. A history of allergy is uncommon. In those cases (10% to 15%) with associated squamous cell carcinoma, the carcinoma usually is present at the time of initial diagnosis, rather than occurring at the time of recurrence of previously resected inverted papilloma.[52]

Inverted papilloma is most common in the 40- to 70-year age-group. It is rare in childhood and adolescence.[18] Men outnumber women about 3 : 1 to 4 : 1.

Unexplained hyponatremia, apparently secondary to inappropriate secretion of antidiuretic hormone, has led to the diagnosis of esthesioneuroblastoma in several reported patients.[66,70,74,78] Successful treatment in two of the reported cases led to resolution of the electrolyte abnormality, as it did in one patient from the University of Florida. Interestingly, all four patients for whom information was available (three from the literature, one from the University of Florida) were women. Despite the presence of intracytoplasmic neurosecretory granules and the histochemical, biochemical, and structural similarities between olfactory and childhood neuroblastomas, the authors are not aware of reports documenting elevated urinary secretion of dopamine, vanillylmandelic acid, or homovanillic acid in esthesioneuroblastoma.[15]

Patients with polymorphic reticulosis or lethal midline granuloma have nasal cavity involvement in 90% of cases, often with extension to the paranasal sinuses, nasopharynx, palate, and orbit. Erosion to the skin surface may occur. Perforation of the nasal septum or hard palate is common. Lymph nodes are involved at presentation in 10% of cases, and later become involved in another 10%. Nasal obstruction is the common early symptom. Almost two thirds of patients have weight loss, fevers, and night sweats (B symptoms, suggestive of a lymphoproliferative disorder). Eventually, a diffuse histiocytic lymphoma occurs in some patients. Men are affected two to three times more commonly than women. The median age is in the fifth decade.[71]

PHYSICAL EXAMINATION. The nasal cavity is inspected via nasal speculum examination and examination with a 30-degree rigid fiberoptic nasoscope after topical anesthesia and shrinkage of the mucosa. The cranial nerves are examined. Evidence of tumor extension into the orbit is sought by simultaneously palpating the orbits with the index fingers; the tips of the fingers are placed between the bony orbital wall and the eyeball, and the findings are compared with the normal side. A 90-degree Hopkins laryngopharyngoscope provides a better view of the nasopharynx and posterior nares than a mirror, and a much better panorama than either rigid or flexible nasoscopes, which have relatively constricted fields of view.

Maxillary Sinus

Squamous cell carcinoma is the most common cancer of the maxillary sinus (60% to 70%), followed by adenoid cystic carcinoma (15% to 20%).[26]

Maxillary sinus cancers tend to remain silent as long as they are confined to the sinus; they produce symptoms once they extend outside the sinus. Seventy-five percent to 80% of patients have advanced (T3–4) disease at presentation. Sixty percent have orbital invasion at presentation.[26] Nasal obstruction, nasal discharge, epistaxis, "sinus pain," and a sensation of fullness over the involved antrum all are common. Proptosis, diplopia, and chemosis may result from orbital invasion. A mass may develop in the cheek or temporal region. Posterior tumor extension produces trismus and headache secondary to invasion of the pterygoid muscles and the base of the skull. Cranial nerve deficits may result from invasion of the base of the skull or infraorbital nerve in the floor of the orbit, resulting in paresthesia or anesthesia of the skin of the upper lip, side of the nose, and anterior premaxillary skin. Inferior tumor extension leads to complaints of pain and loosening of the upper teeth. Frequently, patients consult a dentist, and teeth may be

extracted without relief of pain. If patients are edentulous, submucosal tumor extension often causes improper fitting of dentures. Ulceration of the mucosa generally follows and may lead to an oral–antral fistula in the region of the gingivobuccal sulcus or upper gum.

PHYSICAL EXAMINATION. Clinical examination should independently address the possibility of anesthesia in each of the following areas, because each has specific implications regarding tumor spread: upper lip and lateral nose (infraorbital nerve); buccal side of the posterior alveolus in the area of the premolar and molar teeth (posterior superior alveolar nerve); canine and incisor teeth and adjacent gums (anterior superior alveolar nerve); and hard palate (greater palatine nerve). If the incisor teeth and upper lip are both numb and no mass is palpable in the gingivobuccal sulcus, one can predict that tumor involves the orbital floor. Numbness of the incisor teeth may be a result of destruction of the anterolateral wall of the maxillary sinus, or if patients have had a Caldwell-Luc procedure, the procedure itself may be responsible. Because the infraorbital nerve is slightly lateral to the midline in the orbital floor, it is possible to have destruction of the medial floor of the orbit without nerve involvement. Hemipalatal anesthesia may result from invasion of the pterygopalatine fossa (in which case tearing may also be absent because of involvement of the secretomotor fibers from the sphenopalatine ganglion to the lacrimal gland) or from invasion of the greater palatine nerve, which is in close proximity to the posterior inferior nasal wall of the sinus. These nerves run in the greater and lesser palatine foramina, which are visible on both axial and coronal images. Loss of sensation in the posterior alveolus or molar and premolar teeth suggests cancer in the infratemporal wall. Unless the maxillary nerve is also involved, sensation of the face remains intact. The palatal aspect of the gums is supplied by the greater palatine nerve, so posterior superior alveolar nerve function must separately be tested on the buccal side of the alveolus.[57] Signs of orbital invasion, cranial nerve involvement, and soft tissue extensions over the face or temporal fossa are especially important. The maxillary teeth, gingivobuccal sulcus, alveolus, and hard palate should be inspected and palpated.

Submucosal fullness on the posterolateral pharyngeal wall may occur from primary tumor extension via the nasopharynx, but is more likely due to retropharyngeal lymph node metastases.

Ethmoid Sinus

Mild to moderate sinus ache or pain referred to the frontal, nasal, or retroorbital area is an early symptom of tumors of the ethmoid sinus.

Because the ethmoid air cells extend far anteriorly, tumor may appear initially as a subcutaneous nodule in the inner canthus. The mass may be interpreted by patients as a boil, or by physicians as dacryocystitis, resulting in inappropriate incision and drainage. Diplopia, proptosis, and a palpable orbital mass are common. Nasal discharge, epistaxis, and obstruction also are frequent.

Sphenoid Sinus

Cranial nerve palsies (ptosis and paralysis of extraocular muscles) and headache usually are the first symptoms of sphenoid sinus cancer. Diagnosis often is delayed until tumor involves the nasopharynx or nasal cavity, where it can be seen and is accessible for biopsy.

METHODS OF DIAGNOSIS AND STAGING

Biopsy usually is performed on tumor in the nasal cavity, oral cavity, nasopharynx, medial canthal area, or through a Caldwell-Luc incision into the maxillary sinus. Frontal sinus tumors are approached by frontal sinus trephination.

Diagnostic Imaging

Computed tomography (CT) and magnetic resonance imaging (MRI) are used for the majority of tumors of the sinonasal area. Plain films have little value outside of portal planning and to evaluate dentition. Angiography plays a small adjunctive role in the odd hypervascular lesion or, at times, as a prelude to infusion chemotherapy or preoperative embolization. Ultrasound plays no role.

Examination Technique

Sinonasal CT and MRI should be done in the axial *and* coronal planes. Coronal sections are essential for evaluating the anterior skull base, floor of the orbit, and cavernous sinus. Axial sections are best for detecting spread to the orbital apex, pterygopalatine fossa, infratemporal fossa, and face. Sagittal MRI is useful for evaluating the inner table of the frontal sinus, the cribriform plate, and the anterior wall and floor of the middle cranial fossa.

Sections should always be 3 mm thick or less; 5-mm thick sections are *not acceptable* in patients with known sinonasal cancer, unless extenuating circumstances exist. Sections measuring 1 to 2 mm thick may be used in critical areas of interest.

Intravenous contrast is almost always used with CT and MRI, since it is of prime value in the search for intracranial spread and in determining whether sinuses are obstructed or invaded.

The lymph nodes are not routinely studied in sinonasal cancer. The neck is surveyed if tumor has spread into the soft tissues of the face or mucosa of the nasopharynx, if positive retropharyngeal or facial nodes are present, and for high-grade lesions.

A metastatic workup may be done in advanced lesions.

Imaging of the Normal Anatomy

The normal anatomy of the sinonasal region is demonstrated in Figures 22-9 through 22-12. A clear understanding of the pterygopalatine fossa and its relationship to the inferior orbital fissure, infratemporal fossa, sphenopalatine foramen, and foramen rotundum is essential.[42]

The differences between the CT and MRI rendering of bone detail are discussed in Chapter 4. Considerable variation exists in the thickness of bone within the paranasal sinuses. The seeming absence of bone on CT does not necessarily indicate bone destruction. The thin walls of the ethmoid air cells are particularly troublesome, tending to disappear whenever the sinuses are filled with material other than air. The same is true of the medial

(*text continues on page 568*)

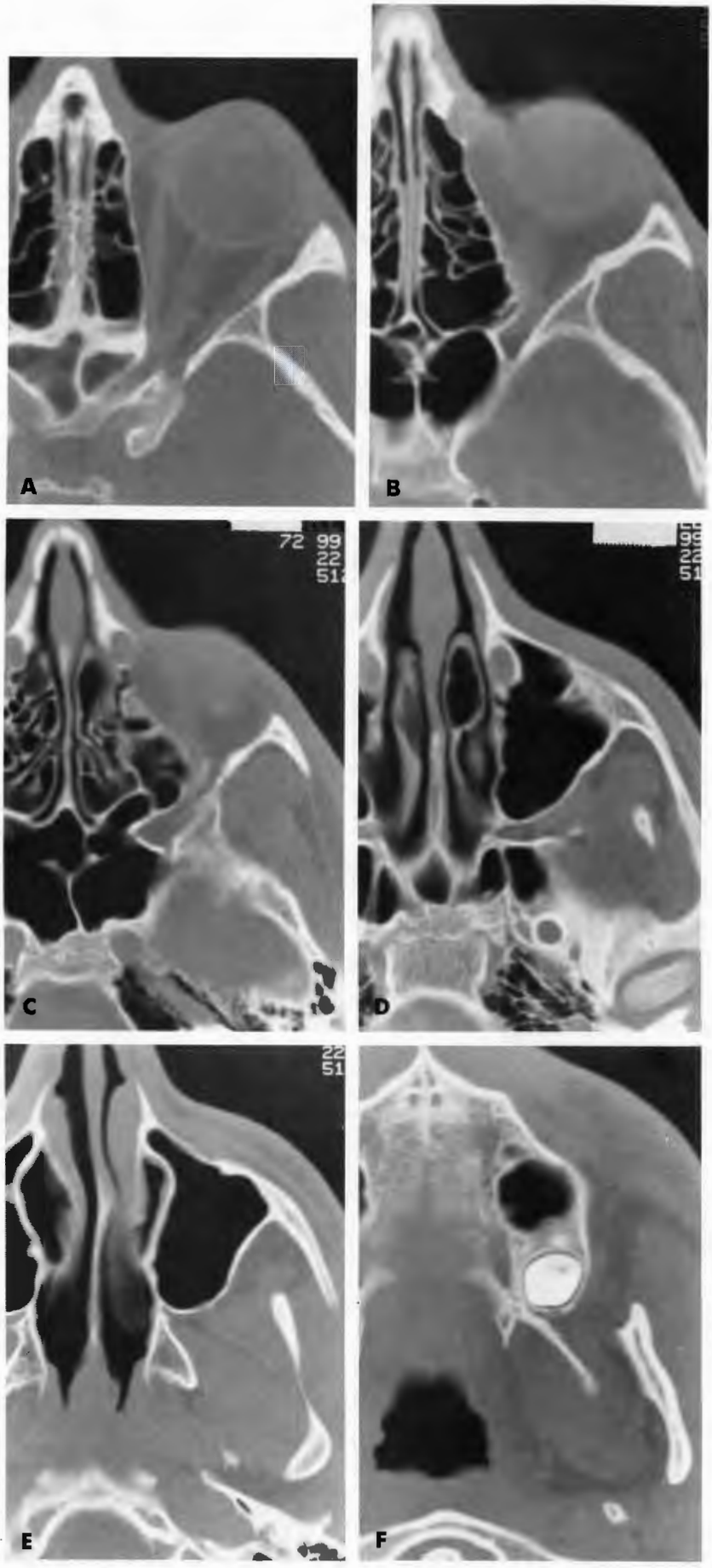


Figure 22-9. (*A* through *F*) CT of normal anatomy of the face and paranasal sinuses in the axial plane. (Modified from Mancuso AA, Harnsberger HR, Dillon WP. Workbook for MRI and CT of the head and neck, ed 2. Baltimore, Williams & Wilkins, 1989:60–61)

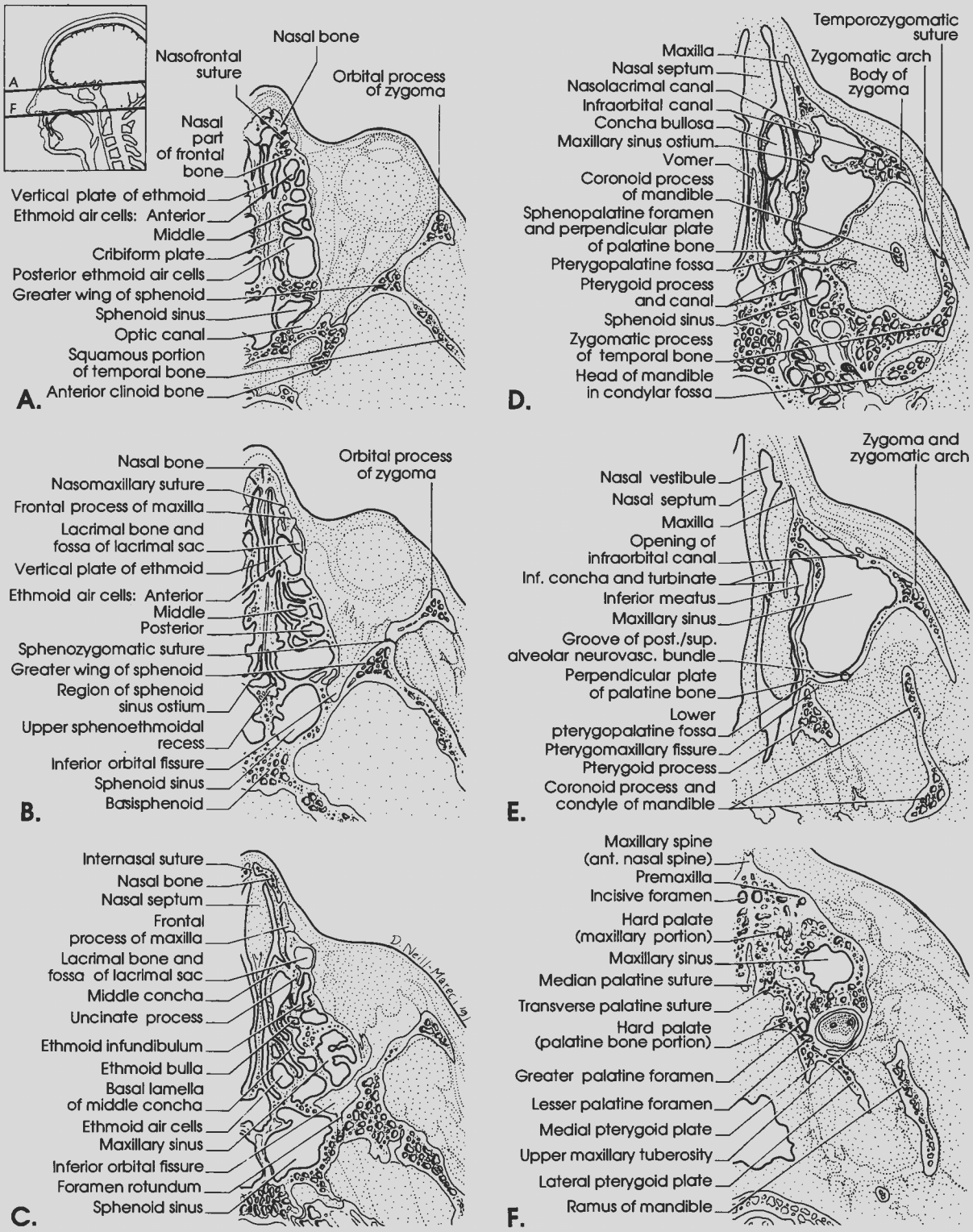


Figure 22-10. (*A* through *F*) Line diagrams correlating with anatomy seen in Figure 22-9. (Modified from Mancuso AA, Harnsberger HR, Dillon WP. Workbook for MRI and CT of the head and neck, ed 2. Baltimore, Williams & Wilkins, 1989:60–61)

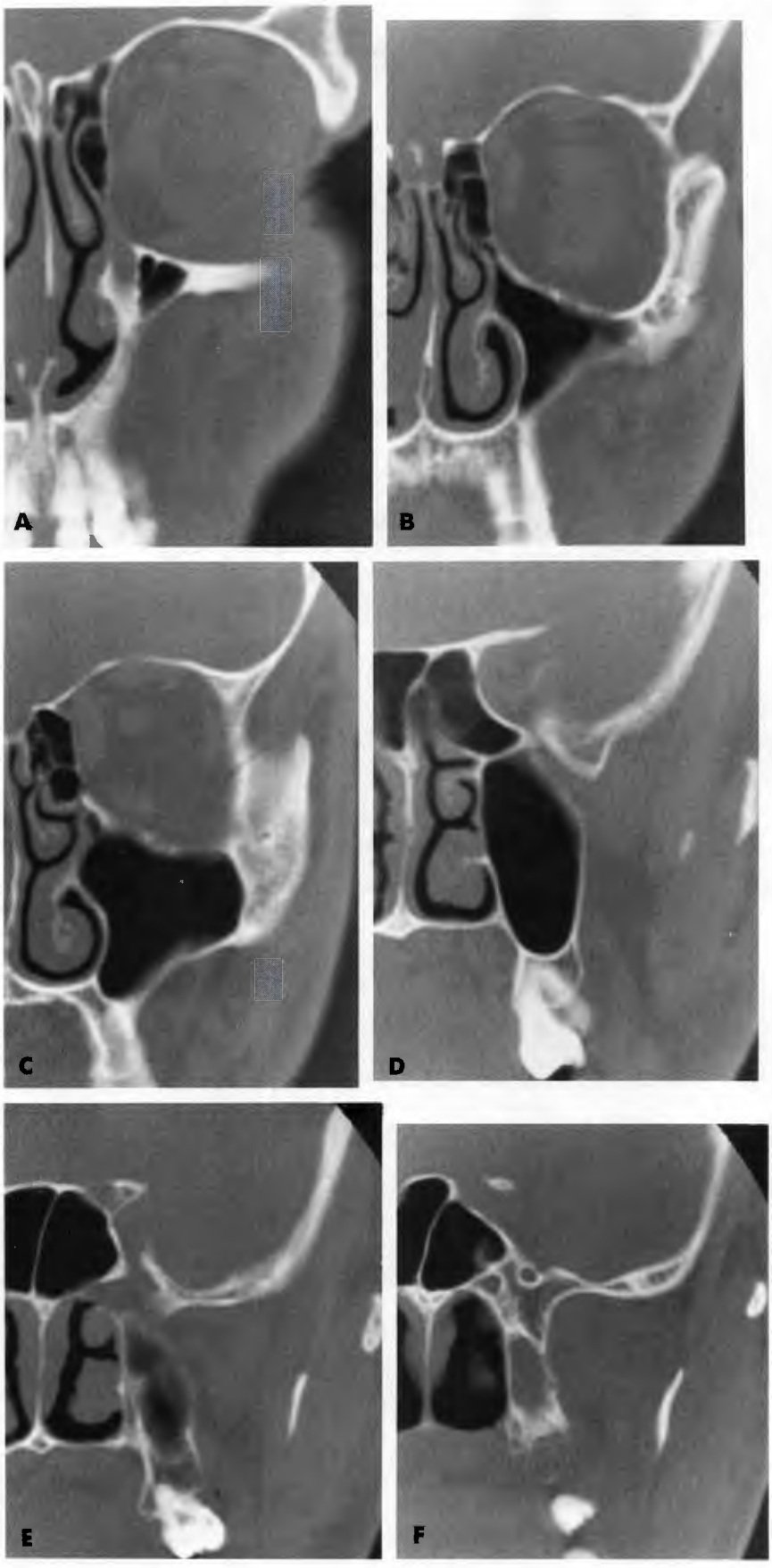


Figure 22-11. (*A* through *F*) CT of normal anatomy of the face and paranasal sinuses in the coronal plane. (Modified from Mancuso AA, Harnsberger HR, Dillon WP. Workbook for MRI and CT of the head and neck, ed 2. Baltimore, Williams & Wilkins, 1989:60–61)

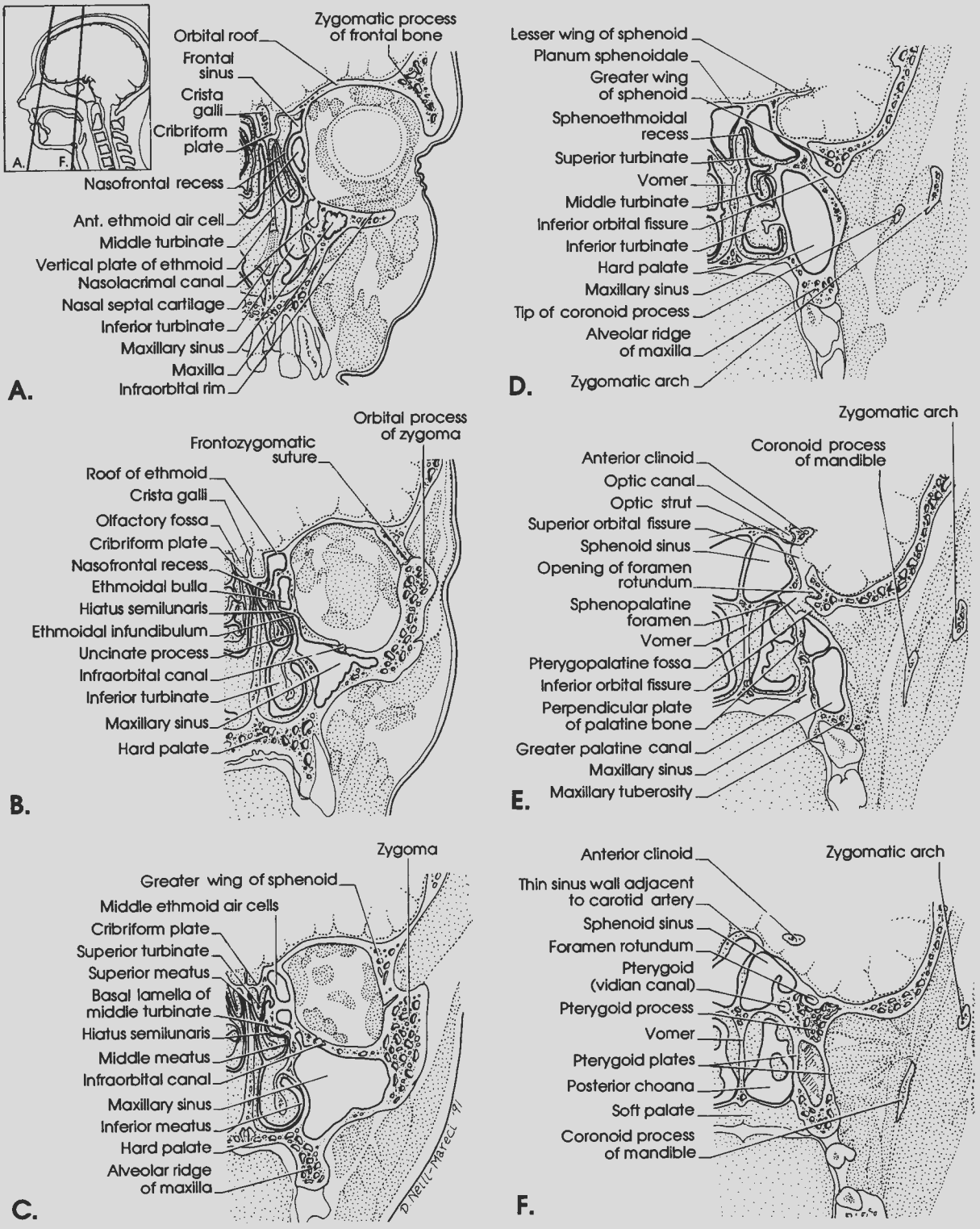


Figure 22-12. (*A* through *F*) Line diagrams correlating with anatomy seen in Figure 22-11. (Modified from Mancuso AA, Harnsberger HR, Dillon WP. Workbook for MRI and CT of the head and neck, ed 2. Baltimore, Williams & Wilkins, 1989:60–61)

wall of the maxillary sinus; broad portions of this wall normally are not ossified.

Another anatomic variant that leads to some diagnostic confusion is the fact that the maxillary antrum projects into the posteromedial floor of the orbit on axial images. Of course, the sinus is not within the orbit, it only appears to be because of the conical shape of the orbit. Inexperienced interpreters sometimes will mistakenly think that abnormalities in the posteromedial aspect of the maxillary sinus are in the orbit. The true relationship of sinus structures to the orbital floor is best depicted on coronal and sagittal images.

The normal variations in the cycle of blood flow to the nasal turbinates may make them appear considerably larger on one side of the nasal cavity. This occasionally makes the task of defining the extent of a mass in the nasal cavity more difficult. The nasal mucosa can be sprayed with vasoconstrictors before MRI or CT to eliminate the problem.

When evaluating perineural spread of tumor along the infraorbital nerves or within the pterygopalatine fossa and foramen rotundum region, normal perineural enhancement should not be confused with pathologic enhancement of the nerve. This is more problematic as one gets closer to the exit foramina of these nerves at the skull base, with normal perineural enhancement being most prominent in the foramen rotundum and foramen ovale. Careful comparison of the possibly abnormal to the uninvolved side sometimes is required to detect subtle perineural spread and to avoid diagnosing normal variations of perineural enhancement as evidence of perineural involvement with tumor.

Indications for Study

Virtually all sinonasal cancers are studied with CT or MRI or both. MRI is also recommended in most cases of nasal vestibule cancer, except for limited T1 lesions, because of the tendency for more extensive spread than suggested by physical examination. All advanced nasal vestibule tumors should be studied to look for bone involvement.

Our preference is to use CT as the first examination with MRI reserved to answer any remaining questions. Both studies are required in over half of the patients who have sinonasal cancer or a benign aggressive lesion. Most patients already have had CT for evaluation of what was believed to be benign sinus disease by the time cancer is diagnosed. The most common reasons for adjunctive MRI are as follows:

1. Evaluating the paranasal sinus—dural interface, usually at the anterior skull base, but sometimes in the cavernous sinus or anterior wall and floor of the middle cranial fossa
2. Evaluating spread through the dura into the leptomeninges or brain
3. Determining whether sinuses are filled with tumor, fluid, or secondary inflammatory mucosal changes
4. Looking for subtle perineural extensions, including involvement of the cavernous sinus
5. Determining the extent of tumor relative to the orbit
6. Defining the limits of spread in the soft tissues of the face or the infratemporal fossa

Imaging with CT and MRI is useful in evaluating the following specific areas and issues of interest:

DIFFERENTIAL DIAGNOSIS. In general, the various histologic types of tumors that arise in the sinonasal area have no specific CT or MRI appearance. Inflammatory polyps and salivary gland tumors tend to be brighter on T2-weighted MRI than most cancers (see Chap. 4, Figs. 4-7 and 4-8). An aggressive pattern of bone destruction and infiltrative growth strongly suggests cancer (Fig. 22-13). A pattern of expansion or bone remodeling suggests a benign neoplasm, low-grade malignancy, or coexistent mucocele. Identification of a calcifying or ossifying matrix is useful in identifying the relatively uncommon osteosarcomas and chondrosarcomas that affect the facial bones and, secondarily, the sinuses. (See Chap. 4, Fig. 4-8.) Multiplanar imaging might also show findings suggesting a dental origin of the lesion, rather than an origin in the paranasal sinuses. A hypervascular pattern seen on MRI may lead to earlier recognition of unusual masses such as hypervascular metastases or hemangiopericytoma; recognizing potential hypervascularity before biopsy may also avoid excessive blood loss. Rarely, intracranial lesions or developmental anomalies such as meningoencephalocele can mimic neoplasms in their presentation. Proper imaging will help to avoid inadvertent entry into the cranial vault during diagnostic or therapeutic procedures. A necrotizing, excavating growth pattern seen on CT or MRI with little obvious mass strongly suggests midline granuloma as the diagnosis (Fig. 22-14).

INTRACRANIAL SPREAD. The likely location for intracranial extension depends mainly on the site of origin of the lesion. Anterior skull base invasion is best demonstrated with coronal and sagittal sections (Figs. 22-15 and 22-16). Coronal sections also are useful to detect involvement of the cavernous sinus and parasellar regions, as well as the medial aspects and floor of the middle cranial fossa. Axial images are most useful to detect posterior spread to the middle cranial fossa via the orbital apex and superior or inferior orbital fissures (Fig. 22-17). Focused sagittal images may reveal early invasion of the anterior and inferior aspects of the middle cranial fossa.

The earliest sign of intracranial invasion is bone erosion at the sinus—dural interface; this is best detected on CT. However, MRI is the single best study to evaluate tumor spread beyond early cortical bone invasion (see Fig. 22-13). The overlying dura will often appear thickened and will be enhanced when invaded by tumor. Dural enhancement may be only a reaction to adjacent tumor. Frequently, dural reaction (enhancement) beyond the actual site of the dural invasion is present. Irregular thickening of the dura strongly indicates involvement and possible penetration, and suggests continued spread into the subdural or subarachnoid space (see Fig. 22-13). The earliest sign of brain invasion is enhancement of the surface of the brain and localized edema in the same region (see Fig. 22-13). An obvious mass invading the brain is seen in cases of advanced brain involvement (see Fig. 22-15).

ORBITAL INVOLVEMENT. Coronal sections are best for evaluating the floor and roof of the orbit. A combination of axial and coronal images is essential for evaluating the medial, lateral, and posterior orbital walls. Sagittal images are only used adjunctively. The earliest sign of orbital invasion is erosion of cortical bone and displacement of extraconal orbital fat (Fig. 22-18). At times it is not possible to determine whether the tumor has crossed the periorbit to involve the extraconal fat

Figure 22-13. Patient with poorly differentiated carcinoma of the sinonasal region, probably arising in the ethmoid region. (*A*) Contrast-enhanced, T1-weighted MRI shows tumor (T) invading the ethmoids and nasal cavity bilaterally, the medial wall of the orbit (*arrowhead*), and roof of the ethmoid (*open arrow*). Note the interface between the invading cancer and mucosal thickening (M) in the maxillary sinus. The orbital spread involves the extraconal fat, but at this point spares the muscle cone. (*B*) T2-weighted MRI shows the tumor (T) clearly much lower in signal than the mucosal thickening (M) in the maxillary sinus and ethmoid on the opposite side. The dura appears to be intact (*arrow*) at the point of invasion of the anterior skull base. The adjacent brain (B) is not edematous. (*C*) Coronal CT, a little more posterior than the MRI seen in *A*, shows aggressive bone destruction of the anterior skull base at the junction of the ethmoid roof and planum sphenoidale (*arrow*), perpendicular plate of the ethmoid (*arrowhead*), and medial wall of the orbit (*open arrow*). (*D*) Coronal, contrast-enhanced, T1-weighted MRI at nearly the same level as *C*. The dura is irregularly thickened and is enhanced (*arrowheads*). The appearance *suggests* dural penetration. (*E*) T2-weighted MRI at the same level as *D*. The displaced dura is *not* seen (*arrowheads*) as it was in *B*, supporting the possibility of full-thickness dural invasion. No definite brain edema is present to confirm brain invasion. Arachnoid or pial involvement cannot be excluded, however.

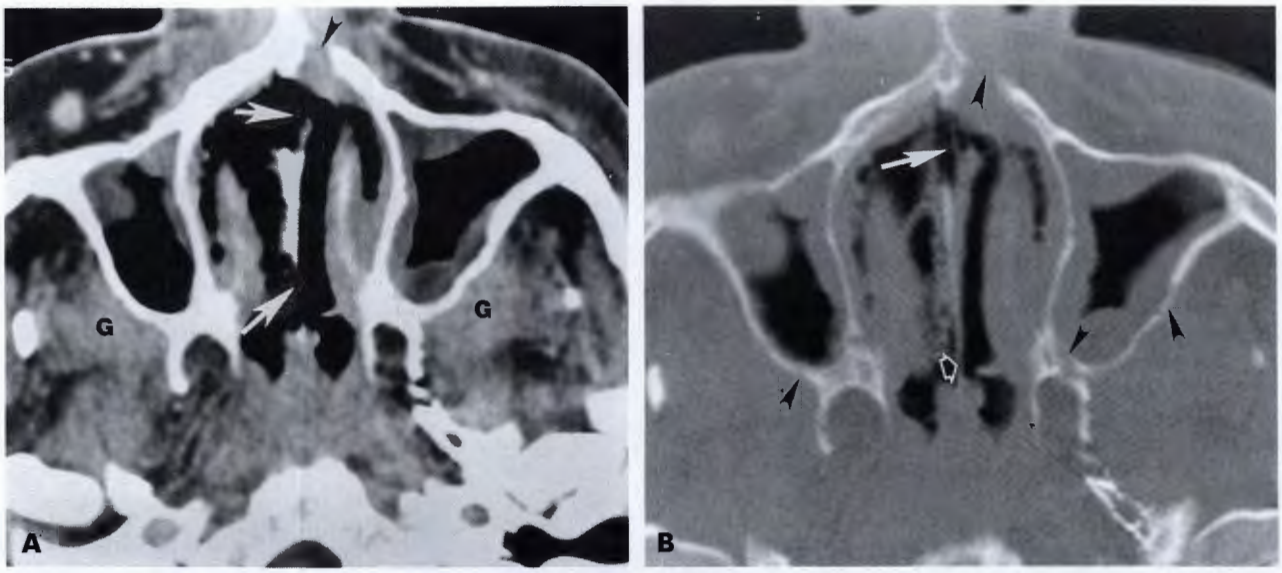


Figure 22-14. A patient with midline granuloma. (*A*) Axial CT, photographed for soft tissue detail, shows areas of potential erosion in the anterior and posterior nasal septum (*arrows*). Mucosal thickening lines the nasal cavity with a focal erosion of the premaxilla (*arrowhead*). The retroantral fat is invaded bilaterally by the infiltrating granulomatous tissue (G). (*B*) Same level as section *A* filmed for bone detail. Numerous areas of bone erosion are confirmed (*arrowheads*) adjacent to soft tissue findings described in *A*. The nasal septum is perforated anteriorly (*arrow*) and markedly thinned posteriorly (*open arrow*).

(see Fig. 22-16). Once the lesion has entered the orbital fat, it is difficult, at times, to be sure whether it has penetrated the muscle cone. Findings on even high-quality CT and MRI need to be confirmed at the time of surgery before the surgeon can decide whether orbital exenteration is necessary.

A combination of CT and MRI is extremely useful for evaluating spread to the lacrimal bone, lacrimal sac, and nasolacrimal duct, and within preseptal soft tissues (see Fig. 22-18). Detailed imaging usually can determine the relationship of tumor to deeper structures of the eyelid, and show early spread through the orbital septum.

SPREAD TO THE INFRATEMPORAL FOSSA. This is best studied with axial sections. The earliest sign of spread to the infratemporal fossa is erosion of the cortical bone along the posterior wall of the maxillary antrum (Fig. 22-19). This is often seen near the groove of the posterior superior alveolar neurovascular bundle. Obliteration of the tissue planes posterior to the antrum and around the distal maxillary vessels in the retroantral fat pad are other early signs of infratemporal fossa spread. Continued extension will produce obvious mass effect extending from the retroantral fat into the muscles of mastication (see Fig. 22-17). Spread through the posterior wall of the antrum and into the infratemporal fossa can also extend into the inferior orbital fissure and directly laterally into the soft tissues of the face.

SPREAD TO THE NASOPHARYNX. Sinonasal cancers frequently bulge through the posterior choanae to the nasopharyngeal portion of the airway. Imaging can help determine whether tumor merely bulges into the nasopharynx or actually invades its walls.

SPREAD TO THE SUBCUTANEOUS FAT. In advanced cancers, spread through the anterior wall of the sinus or laterally may be detectable clinically. Axial images, in particular, are useful for showing early extension through the bony confines of the maxillary antrum to the subcutaneous fat. These studies can also demonstrate penetration of tumor beyond the platysma or muscles of facial expression to subcutaneous fat, a finding which suggests that the dermal lymphatics may be involved. In these cases, the imaging examination is extended to include all of the facial, parotid, submandibular, and submental nodes and the upper internal jugular nodes (see Chap. 6).

PERINEURAL SPREAD OR SPREAD ALONG THE NEUROVASCULAR BUNDLES. This finding may drastically alter the prognosis and therapy in patients with sinonasal cancer. Imaging findings indicating perineural spread may be present without correlative physical findings or symptoms. Until the development of high-resolution, contrast-enhanced MRI, the main findings on imaging studies to indicate perineural spread were (1) enlargement of the nerve, (2) erosion of the facial or skull base bone along the course of the involved nerve, and (3) obliteration of soft tissue planes around the nerve or neurovascular bundle (eg, infiltration of the fat in the pterygopalatine fossa) (Fig. 22-20). Computed tomography often can suggest the proximal extent of spread; however, a normal-appearing course of the nerve or neurovascular bundle does not exclude more proximal extension. MRI with paramagnetic contrast material, and often with fat-suppression techniques, is a definite improvement over CT in that normal sized or minimally enlarged nerves may be suspected of involvement if they are enhanced.

Although MRI is capable of demonstrating tumor involvement of slightly enlarged nerves as far proximally as the brain stem (see Chap. 4, Fig. 4-12), it is not entirely specific in this matter. Reactive or inflammatory en-

hancement secondary to treatment or other incidental disease (eg, viral neuritis) can cause confusion. Also, the nerves at risk may have a perineural vascular plexus, which normally is enhanced. This is especially evident near and within the skull base exit foramina. Particular neurovascular bundles of interest in sinonasal cancer include the olfactory nerves and tract through the cribriform plate and into the anterior cranial fossa; the infraorbital nerve within its canal, as well as its course through the inferior orbital fissure and pterygopalatine fossa to the foramen rotundum; the greater and lesser palatine neurovascular bundles (see Fig. 22-20); the vidian nerve and accompanying vessels; and the posterosuperior alveolar neurovascular bundle as it courses through the retroantral fat, and its more proximal junction with the distal maxillary artery and nerves in the pterygopalatine fossa (see Fig. 22-19). Several of these perineural spread patterns place the cavernous sinus at risk. Coronal, thin-section, contrast-enhanced MRI provides the most definitive evaluation of the cavernous sinus.

FACIAL, PAROTID, RETROPHARYNGEAL, AND CERVICAL LYMPH NODES. These nodal groups are *not* studied routinely in sinonasal cancer. If the tumor involves the nasal cavity, the retropharyngeal, subman-

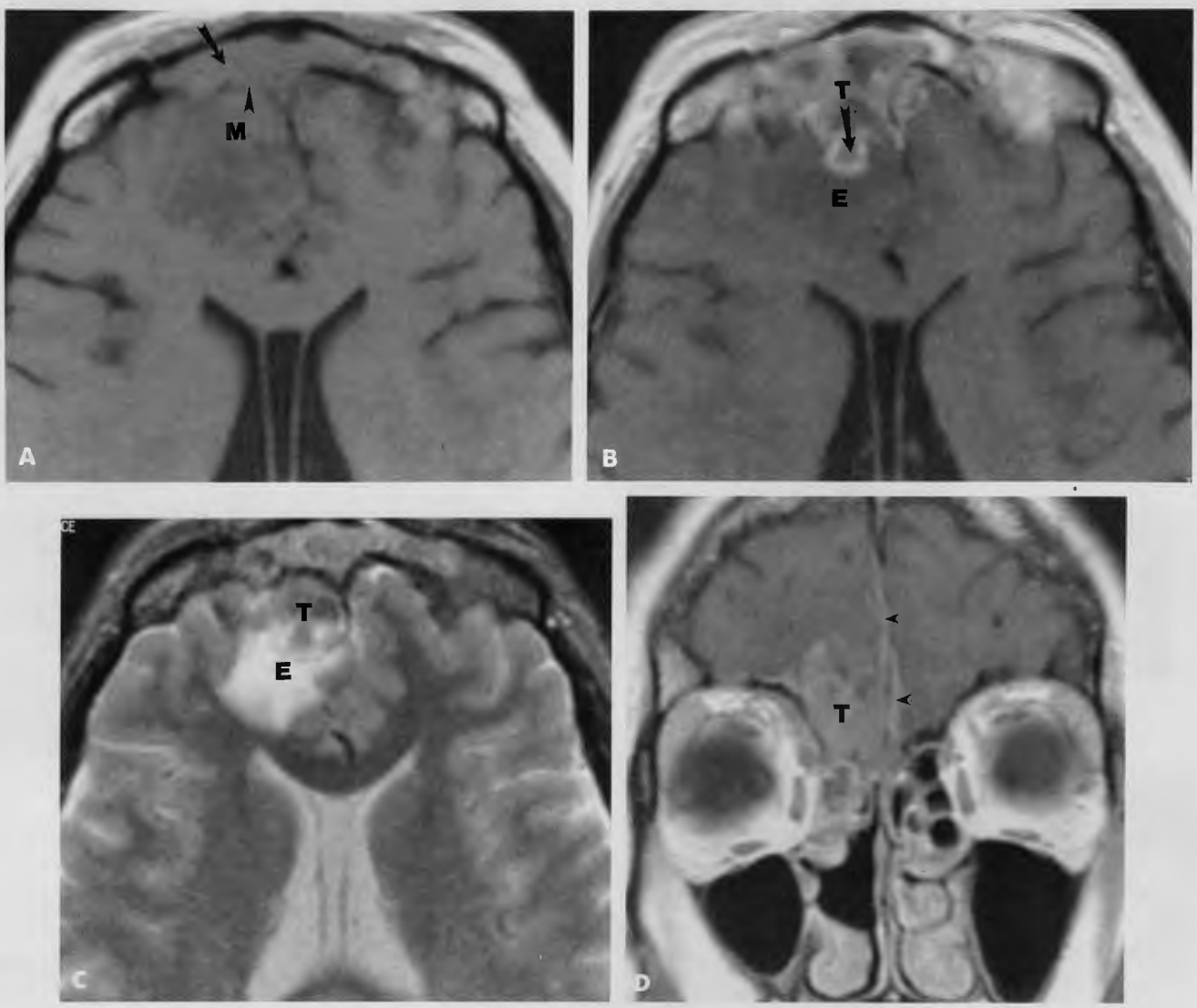


Figure 22-15. Patient with squamous cell carcinoma arising in the anterior ethmoid–frontal sinus region. (*A*) T1-weighted MRI done before injection of paramagnetic contrast medium. Abnormal tissue fills the frontal sinus (*arrow*) and appears to erode its inner table (*arrowhead*); the mass (M) also appears to distort the frontal lobe anatomy. (*B*) T1-weighted MRI (with contrast), at the same level as *A*, shows tumor (T) in the sinus and extending through the inner table into the brain (*arrow*). There is a suggestion of brain edema (E). (*C*) T2-weighted MRI, at the same level (*A* and *B*), shows cancer (T) in the sinus and invading the brain, producing obvious edema (E). (*D*) Coronal, T1-weighted MRI, after injection of paramagnetic contrast medium, shows the relationship of the tumor (T) to the orbit and anterior skull base. The dural enhancement along the anterior falx, just across the midline (*arrowhead*), could be due to tumor invasion or reactive changes.

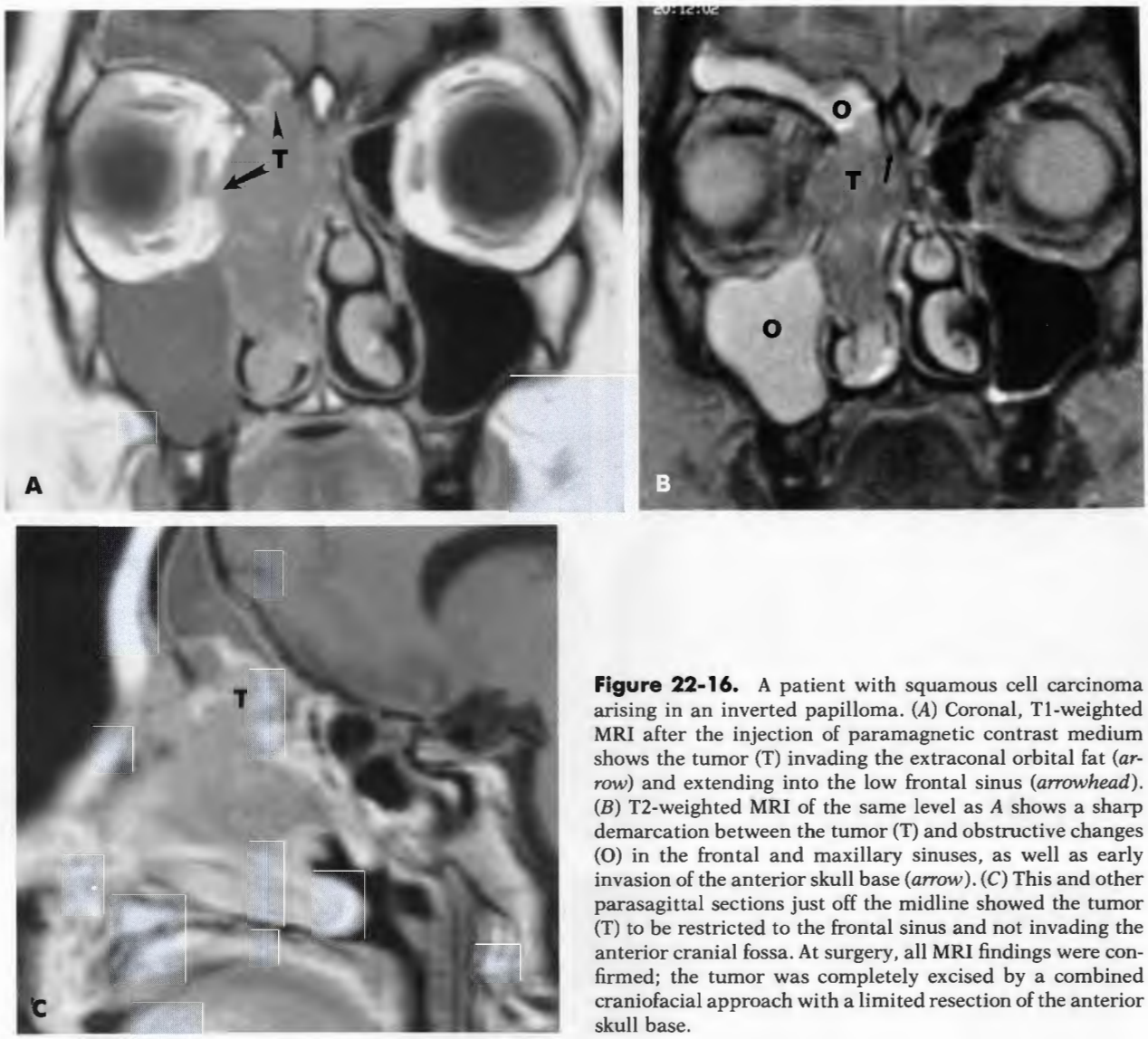


Figure 22-16. A patient with squamous cell carcinoma arising in an inverted papilloma. (*A*) Coronal, T1-weighted MRI after the injection of paramagnetic contrast medium shows the tumor (T) invading the extraconal orbital fat (*arrow*) and extending into the low frontal sinus (*arrowhead*). (*B*) T2-weighted MRI of the same level as *A* shows a sharp demarcation between the tumor (T) and obstructive changes (O) in the frontal and maxillary sinuses, as well as early invasion of the anterior skull base (*arrow*). (*C*) This and other parasagittal sections just off the midline showed the tumor (T) to be restricted to the frontal sinus and not invading the anterior cranial fossa. At surgery, all MRI findings were confirmed; the tumor was completely excised by a combined craniofacial approach with a limited resection of the anterior skull base.

Figure 22-17. A patient with squamous cell carcinoma of the maxillary sinus. MRI was done on a low-field (0.15 Tesla), resistive MRI unit, illustrating that useful MRI studies can be done on low- and mid-field units with proper attention to technical factors. An axial, T1-weighted image shows the tumor invading the orbital apex (T), growing into the greater wing of the sphenoid (compare area between arrowheads with normal side) and the cavernous sinus (*arrow*).

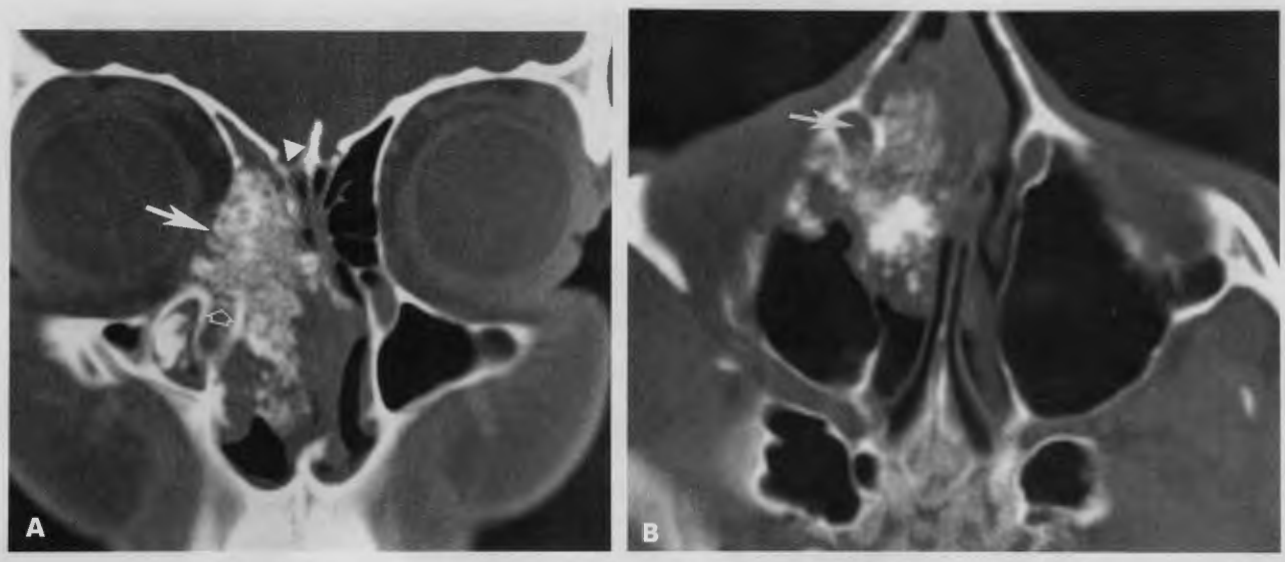


Figure 22-18. A young woman with an esthesioneuroblastoma. (*A*) Coronal CT shows the calcifying tumor centered in the nasal cavity. It destroys the medial orbital wall (*arrow*). This image cannot determine whether the periorbita is invaded, but the lesion did *not* appear to invade the extraconal orbital fat. Also, note that the tumor stops short of the cribriform plate (*arrowhead*) and invades the lacrimal sac and canal (*open arrow*). (*B*) Axial CT shows the extent of tumor within the nasal cavity (middle meatus) and relative to the nasolacrimal canal (*arrow*). (Mancuso AA, Harnsberger HR, Dillon WP. Workbook for MRI and CT of the head and neck, ed 2. Baltimore, Williams & Wilkins, 1989:64)

dibular, submental, and upper neck nodes are studied. If the cancer invades the skin of the face or is recurrent, then the facial, parotid, retropharyngeal, and cervical lymph nodes are potentially at risk and are studied. The lower neck nodes are included only if positive nodes occur in the upper neck or midneck.

Staging Classification

Nasal Vestibule

The American Joint Committee on Cancer (AJCC) system for skin cancer staging is appropriate, since nasal vestibule lesions arise from skin (see the section on staging in Chap. 25) Many reports of nasal cavity carcinoma include the favorable vestibule cases.

Maxillary Sinus

The AJCC staging system applies only to maxillary sinus tumors. Ohngren's line, a theoretical plane joining the medial canthus of the eye with the angle of the mandible, is used to divide the maxillary antrum into the anteroinferior portion (the infrastructure) and the superoposterior portion (the suprastructure). The primary tumor is staged as follows[5]:

TX: Minimum requirements to assess the tumor cannot be met
T0: No evidence of primary tumor
T1: Tumor confined to the antral mucosa of the infrastructure with no bone erosion or destruction
T2: Tumor confined to the suprastructure mucosa without bone destruction, or to the infrastructure with destruction of medial or inferior bony walls only
T3: More extensive tumor invading skin of cheek, orbit, anterior ethmoid sinuses, or pterygoid muscle
T4: Massive tumor with invasion of cribriform plate, posterior ethmoid, sphenoid, nasopharynx, pterygoid plates, or base of the skull

Nasal Cavity and Ethmoid Sinus

The staging system used at the University of Florida for tumors of the nasal cavity and ethmoid and sphenoid sinuses is as follows:

Stage I: Limited to site of origin
Stage II: Extension to adjacent sites (eg, orbit, nasopharynx, paranasal sinuses, skin, pterygomaxillary fossa)
Stage III: Base of skull or pterygoid plate destruction; intracranial extension

The distribution of patients according to stage and primary site is shown in Table 22-2.[56] All seven stage I lesions arose from the nasal cavity.

TABLE 22-2. Distribution According to Stage and Primary Site in 48 Patients

Stages	Nasal Cavity	Ethmoid Sinus	Sphenoid Sinus
I	7	0	0
II	11	8	0
III	13	5	4
Total	31	13	4

(Parsons JT, Mendenhall WM, Mancuso AA, Cassisi NJ, Million RR. Malignant tumors of the nasal cavity and ethmoid and sphenoid sinuses. Int J Radiat Oncol Biol Phys 1988;14:12)

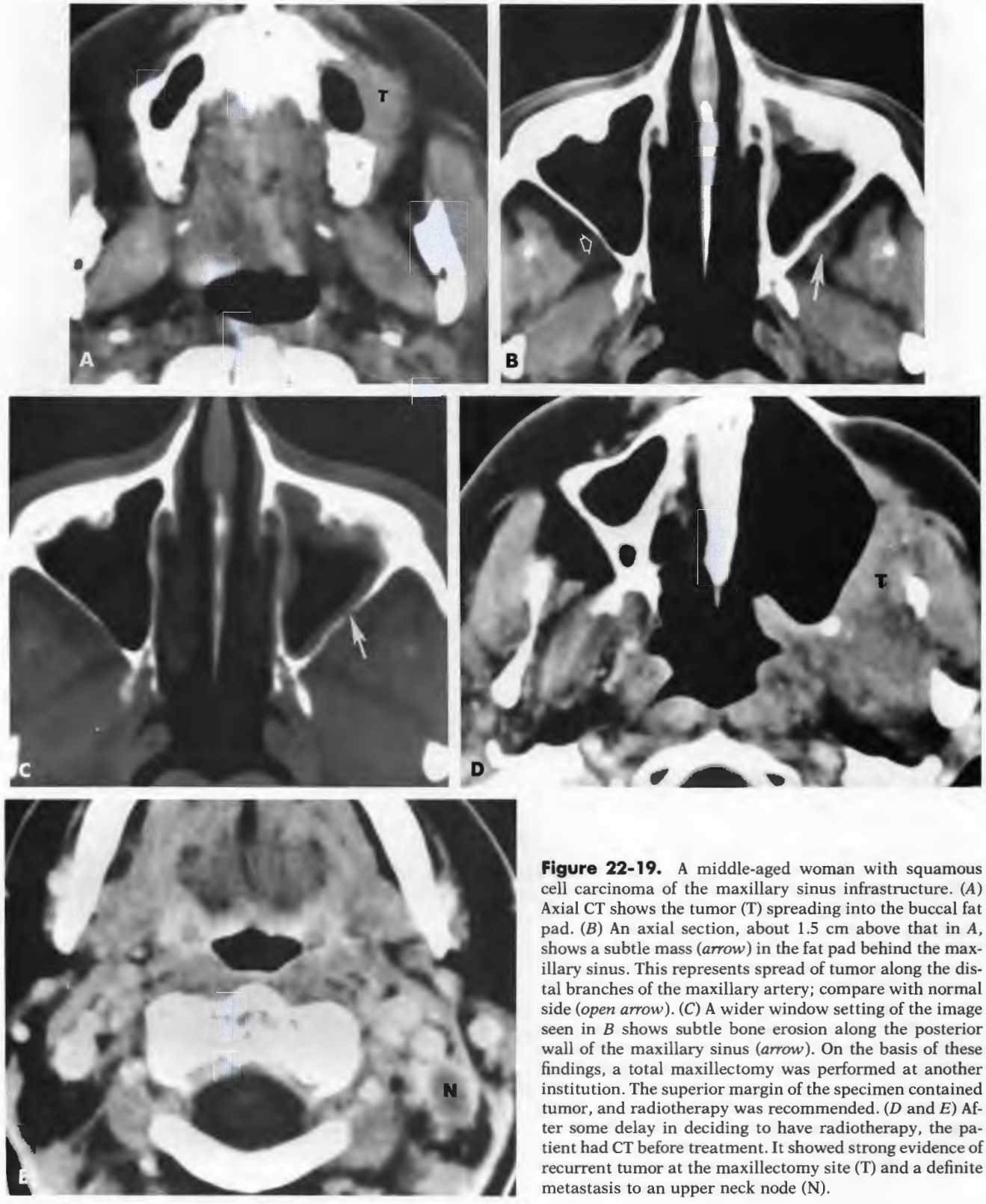


Figure 22-19. A middle-aged woman with squamous cell carcinoma of the maxillary sinus infrastructure. (*A*) Axial CT shows the tumor (T) spreading into the buccal fat pad. (*B*) An axial section, about 1.5 cm above that in *A*, shows a subtle mass (*arrow*) in the fat pad behind the maxillary sinus. This represents spread of tumor along the distal branches of the maxillary artery; compare with normal side (*open arrow*). (*C*) A wider window setting of the image seen in *B* shows subtle bone erosion along the posterior wall of the maxillary sinus (*arrow*). On the basis of these findings, a total maxillectomy was performed at another institution. The superior margin of the specimen contained tumor, and radiotherapy was recommended. (*D* and *E*) After some delay in deciding to have radiotherapy, the patient had CT before treatment. It showed strong evidence of recurrent tumor at the maxillectomy site (T) and a definite metastasis to an upper neck node (N).

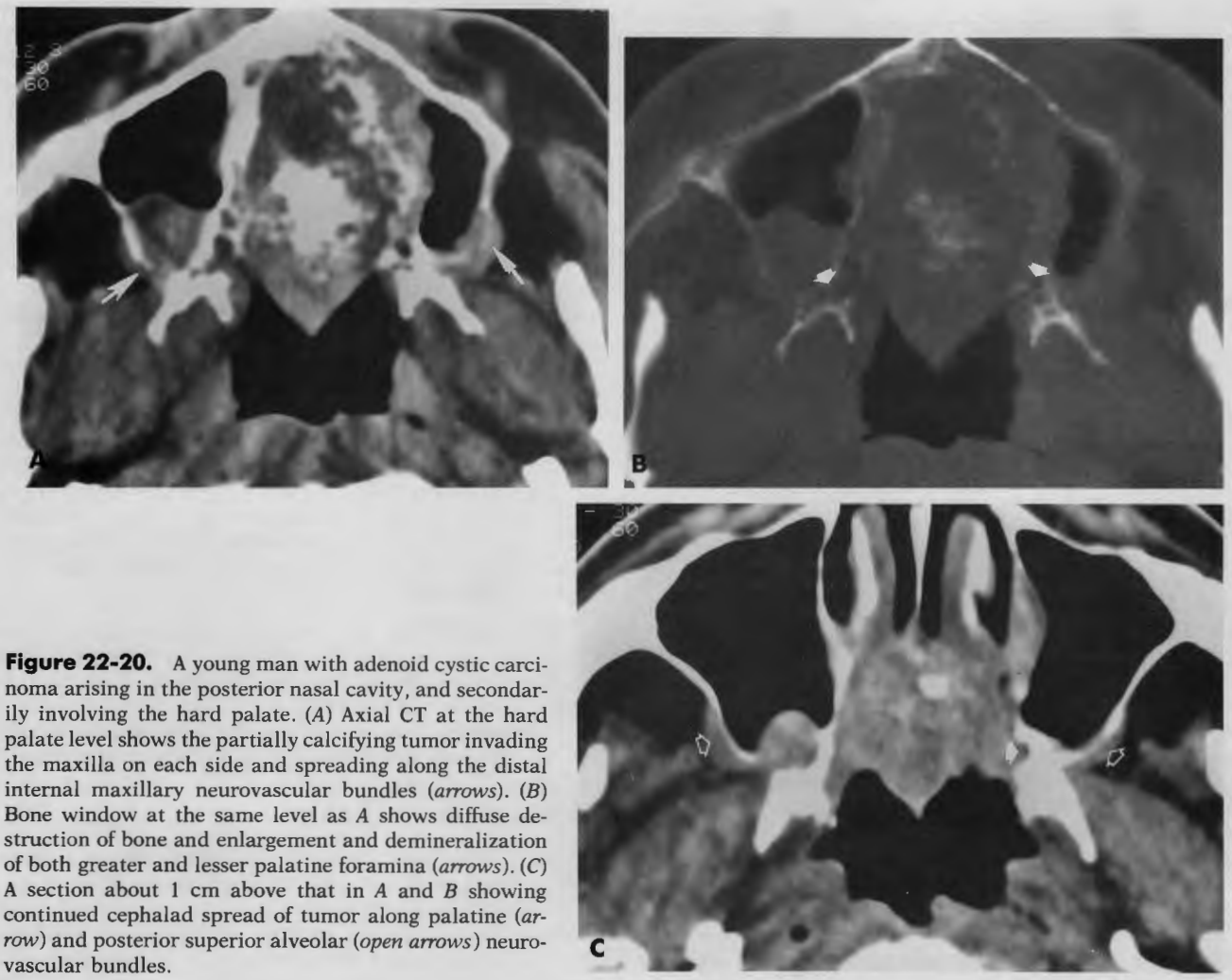


Figure 22-20. A young man with adenoid cystic carcinoma arising in the posterior nasal cavity, and secondarily involving the hard palate. (*A*) Axial CT at the hard palate level shows the partially calcifying tumor invading the maxilla on each side and spreading along the distal internal maxillary neurovascular bundles (*arrows*). (*B*) Bone window at the same level as *A* shows diffuse destruction of bone and enlargement and demineralization of both greater and lesser palatine foramina (*arrows*). (*C*) A section about 1 cm above that in *A* and *B* showing continued cephalad spread of tumor along palatine (*arrow*) and posterior superior alveolar (*open arrows*) neurovascular bundles.

TREATMENT

Nasal Vestibule

Selection of Treatment Modality

Radiation therapy usually is recommended since adequate excision of all but the tiniest of tumors produces deformity. Even apparently early lesions often are deceptively more extensive than they appear. Although locally advanced lesions may be considered for resection followed by radiation therapy, the cosmetic loss from rhinectomy is severe, and, therefore, surgery usually is reserved for salvage after radiation failure. Radiation therapy has been successful in treating surgical failures, but the nasal deformity has already been produced, and the advantage of irradiation is lost.

Although cartilage that has been compromised by tumor invasion, infection, or prior surgery is theoretically more vulnerable to radiation injury, the risk of necrosis is low with properly fractionated external-beam therapy (with or without interstitial implant), even after substantial doses. The probability of tumor control correlates better with tumor volume than with the presence or absence of cartilage invasion.[49]

Surgical Treatment

Excision of lesions in the nasal vestibule usually involves removal of cartilage, as well as skin. Depending on the site of the lesion, either the columella or the alar cartilages will be removed and may be difficult to reconstruct, particularly if the surgery is for radiation therapy failure. If the alar cartilage has been sacrificed, either a composite graft consisting of skin and cartilage from the ear or a nasolabial flap can be used to repair the defect. If the entire external nose is resected, a prosthesis usually is used to cover the defect, since examination for recurrent disease is easier and total nasal reconstruction is cosmetically unacceptable.

Irradiation Technique

Irradiation techniques are not standardized, but success is good with several methods. Selection of technique will depend on the extent of the disease and the experience of the radiation oncologist.

EXTERNAL BEAM. Supervoltage beams are theoretically preferable to orthovoltage in order to reduce the dose in cartilage and adjacent bone. Orthovoltage therapy fractionated over 4 to 6 weeks, however, produces good results; shorter courses with higher daily fractions

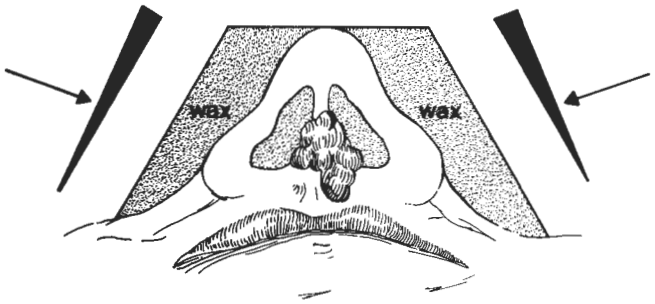


Figure 22-21. Treatment plan for external-beam irradiation of a nasal vestibule carcinoma. (Million RR, Cassisi NJ, Wittes RE. Cancer in the head and neck. In: DeVita VT Jr, Hellman S, Rosenberg SA, eds. Cancer: principles and practice of oncology, ed 2. Philadelphia, JB Lippincott, 1985:483)

will cure the cancer, but the cosmetic result after a couple of years is poor, and the risk of a necrosis is increased.

Two basic supervoltage external-beam treatment plans are used: (1) opposed lateral nasal portals, and (2) an anterior portal with or without lateral portals. When the tumor volume can be encompassed by lateral portals, there is an advantage in avoiding unnecessary exit irradiation to the nasal cavity, nasopharynx, and central nervous system. This technique confines irradiation to the anterior nasal area but has the disadvantage of full skin reaction, since a wax bolus nose block is needed to ensure homogeneous irradiation. The portals may be angled posteriorly to ensure sufficient posterior coverage; wedges are added to compensate for the angle (Fig. 22-21). Fractionation schemes are those used for orthovoltage, since the bolus produces skin reactions comparable to orthovoltage therapy (see Chap. 25). This technique is seldom used for nasal vestibule lesions, but is sometimes used for primary skin cancers of the nose.

The most common external-beam technique uses an anterior portal or portals that are tailored to reduce irradiation of normal tissues. Beeswax or plastic plugs are placed in the nares to fill the air cavities; they act as an electron scattering medium to ensure adequate surface dose and improve dose homogeneity. A tissue-equivalent wax or plastic bolus is placed over the nose to obtain full dose at the skin surface, and also serves to convert the irregular nasal surface to a box-like contour to provide a better scattering medium to underlying tissues[48] (Fig. 22-22). Usually bolus is not used on the tip or bridge of the nose unless it is directly invaded by cancer[48] (Fig. 22-23). Either electrons alone or photons plus electrons may be used for tumor volumes extending from the anterior nasal vestibule to 4 to 5 cm posteriorly. Extensive lesions frequently are managed by external-beam therapy, 5000 cGy over 5 weeks, followed by an interstitial implant (ie, 2500 cGy).

Anterior and lateral portals with wedges may be used when sinus involvement is present (Fig. 22-24). The ipsilateral lymph nodes may be electively irradiated when extensive skin involvement or recurrent disease is present.

INTERSTITIAL IMPLANT. Interstitial implants of the nasal vestibule and nasal cavity are individualized. In our clinic, we have used radium or cesium needles; some other clinics use iridium. The basic implant usually consists of two, three, or four planes of needles inserted through the dorsum of the nose. The basic arrangement to cover the entire nasal vestibule and upper lip is presented in Figure 22-25. Needles may be subtracted for smaller lesions or added for more posterior coverage of the nasal cavity. When the columella is extensively involved, needles at the nasal tip and alar margin are sometimes mounted in rigid nylon bars (two needles per bar). One of the two needles is allowed to lie distal to the nasal tissue (ie, it is suspended in air), thereby extending the volume of the implant beyond the nasal tip so that the columella can be flanked on either or both sides. The technique is particularly useful in patients whose alae have a marked flare; otherwise it would be difficult to extend the high-dose volume far enough inferiorly (Fig. 22-26).

The implant is done with patients under general anesthesia. Postoperative pain and bleeding are tolerable. Computer-generated isodose distributions are essential, since the implant does not comply with basic Paterson-Parker implant patterns. The dose has varied from 5500 to 7500 cGy (depending on the size of the lesion) (Figs. 22-27 and 22-28) when treatment is by interstitial irradiation alone. When combined with external-beam treatment (5000 cGy), the dose from the implant usually is 2000 to 3000 cGy.

NASAL MOLDS. A mold containing a single radium or cesium source may be fashioned for treatment of a small lesion involving one nasal vestibule. Treatment is given on an outpatient basis with applications lasting 1 to 2 hours daily over 7 to 9 days. Few lesions are suitable for this method, which has not been used in our clinic.

Treatment of Lymphatics

The neck usually is observed, when clinically negative, because of the low risk (approximately 15%) of subclinical disease. Elective neck irradiation is used for advanced, recurrent, or poorly differentiated lesions. Patients treated after multiple surgical recurrences may develop in-transit lymph vessel disease; electrons may be used to electively irradiate the transit lymph vessels at risk between the nose and submandibular nodes (the so-called Fu Manchu technique).[47] The match lines should be moved at least once during the course to avoid hot spots.

Management of Recurrence

Lesions recurrent after radiation therapy are excised, and surgical failures usually are treated by radiation therapy. Management of recurrence often is successful, but the cosmetic deformity may be severe. The risk of lymph node metastasis increases with recurrence.

Nasal Cavity and Ethmoid Sinus

Selection of Treatment Modality

Although either surgery or radiation therapy produces high rates of cure for early cancers of the nasal cavity, in the last several years a shift toward primary surgery has occurred at our institution, followed in most instances by postoperative irradiation to a lesser dose than would have been used if radiation therapy alone had been used. The reason for the shift away from high-dose irradiation alone has been to reduce the risk of uni-

(*text continues on page 580*)

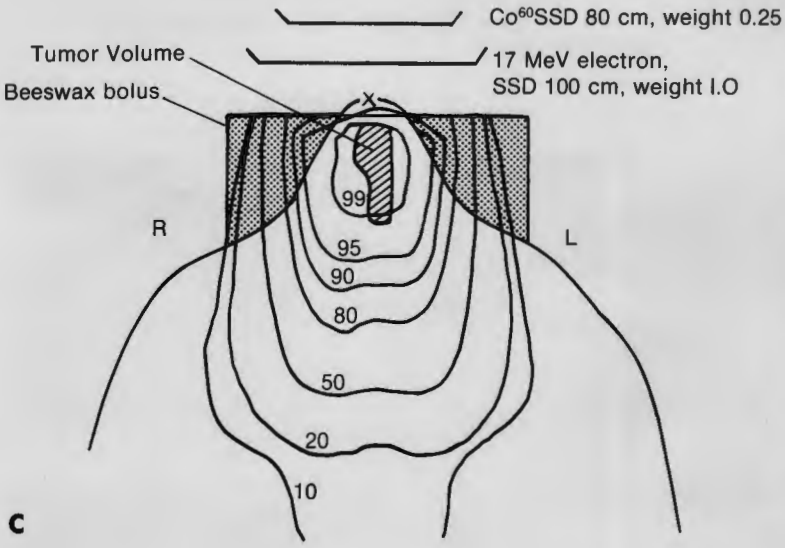


Figure 22-22. A 58-year-old woman with squamous cell carcinoma of the left vestibule that extended into the right vestibule. There was no involvement of the nasal cavity, upper lip, alar cartilage, vestibule floor, or external skin. (*A* and *B*) Left (*A*) and right (*B*) vestibules before treatment. Arrowheads denote the lesion. (*C*) Treatment plan: 17-MeV electron and ^{60}Co anterior open fields with given doses (at maximum dosage [Dmax]) weighted 1 : 0.25. Beeswax bolus was used to compensate for the irregular contour; a bolus was not used on the nasal tip. The SSD (source-to-surface distance) (X) was set on the skin of the tip of the nose. A total dose of 5000 cGy in 18 fractions over 26 days was delivered to the 99% isodose line. A lead shield was placed under the lip during treatment with electrons. (*D*) Skin lines indicating treatment portals: the outer line indicates the electron field, the middle line is the ^{60}Co field, and the inner outlines the tip of nose, where a bolus was not used. (*E*) Three months after irradiation, there was complete tumor regression and excellent cosmetic result. There was no evidence of disease at 8 years. (Mendenhall NP, Parsons JT, Cassisi NJ, Million RR. Carcinoma of the nasal vestibule. Int J Radiat Oncol Biol Phys 1984;10:632–633)

Figure 22-23. A 58-year-old man with T2N0 nasal vestibule cancer. He received 7000 cGy in 37 fractions over 57 days with ^{60}Co and 20-MeV electrons. Arrowheads denote tissue-equivalent beeswax bolus material. Bolus was not used on the skin of the tip of the nose. Wax nasal plugs, which help ensure dose homogeneity, are not visible. The arrow points to the wax-coated lead shield that lies between lip and upper gum and helps shield the oral cavity during electron-beam treatment. A cork attached to a tongue blade depresses the tongue out of the treatment field. (Mendenhall NP, Parsons JT, Cassisi NJ, Million RR. Carcinoma of the nasal vestibule. Int J Radiat Oncol Biol Phys 1984;10:631)

Figure 22-24. (*A*) Squamous cell carcinoma of the left nasal vestibule with direct extension to the skin. Treatment consisted of 7000 cGy over 8 weeks, using ^{60}Co, with anterior and left lateral portals with wedges. The adjacent sinuses were included, and bolus was used on the skin of the nose. The regional lymph nodes were electively irradiated because of the history of rapid growth and skin infiltration. There was 90% regression after 3000 cGy. (*B*) Appearance 3 months after the end of treatment. The patient was free of disease at 5 years.

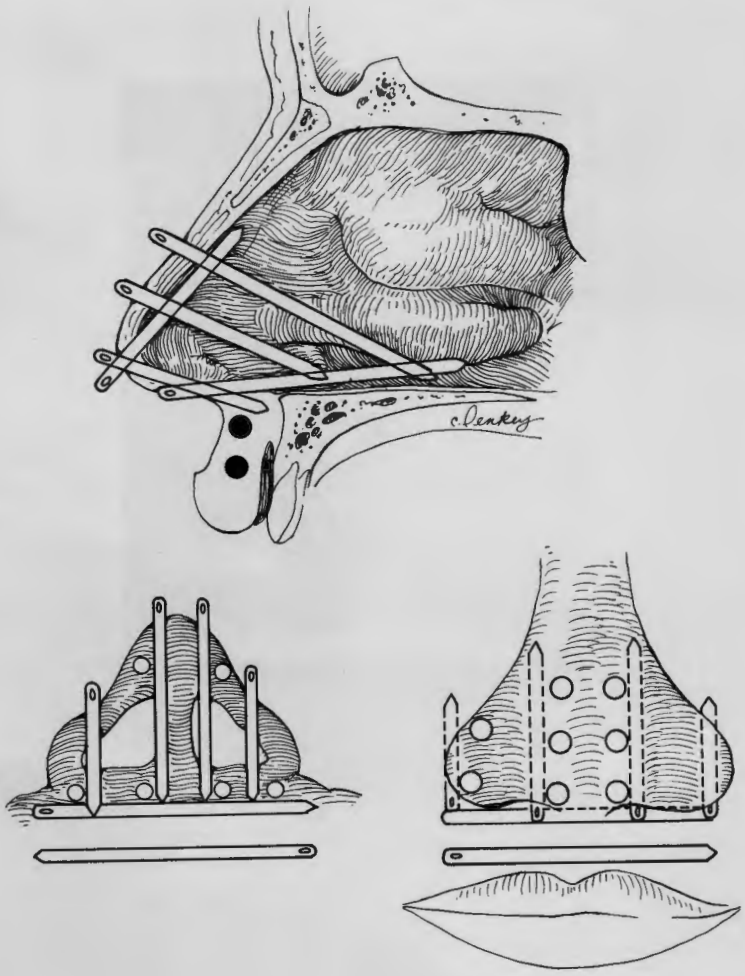


Figure 22-25. Diagram of interstitial implant for carcinoma of the nasal vestibule. The needles near the nasal tip usually are 2 cm active length (3.2 cm physical length) and then progress in a stepwise manner as one proceeds cephalad (3 cm, 4 cm, 4 or 4.5 cm). The superior-most needles sometimes pass through the bones of the nasal dorsum. Varying lengths of the active butts of the needles may be allowed to protrude in order to achieve an adequate dose of irradiation to the tumor periphery. Accurate placement of the needles in the nasal floor often is the most difficult part of the procedure. The needles are inserted until they strike the bony premaxilla. The tips are then "walked" up and over the bone until they can be pushed into place along the nasal floor. At the end of the procedure, each needle is sutured individually into place. (Million RR, Cassisi NJ, Wittes RE. Cancer in the head and neck. In: DeVita VT Jr, Hellman S, Rosenberg SA, eds. Cancer: Principles and practice of oncology, ed 3. Philadelphia, JB Lippincott, 1989:565)

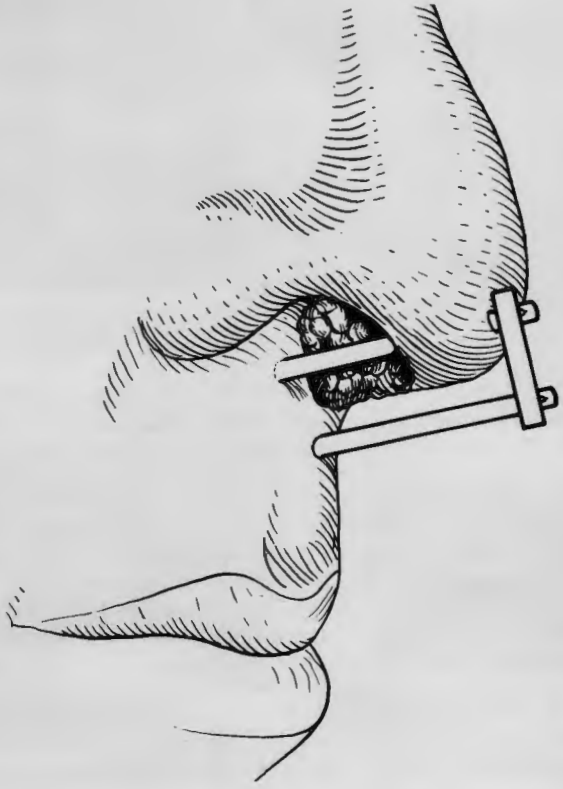


Figure 22-26. The needles near the alar margin and nasal tip are sometimes mounted (two needles to a bar) to rigid implant devices so that the distal needles flank tumor in the columella. The technique is particularly useful if the alae flare significantly in a cephalad direction, since otherwise it would be difficult to extend the implant volume distal enough to ensure adequate dosage.

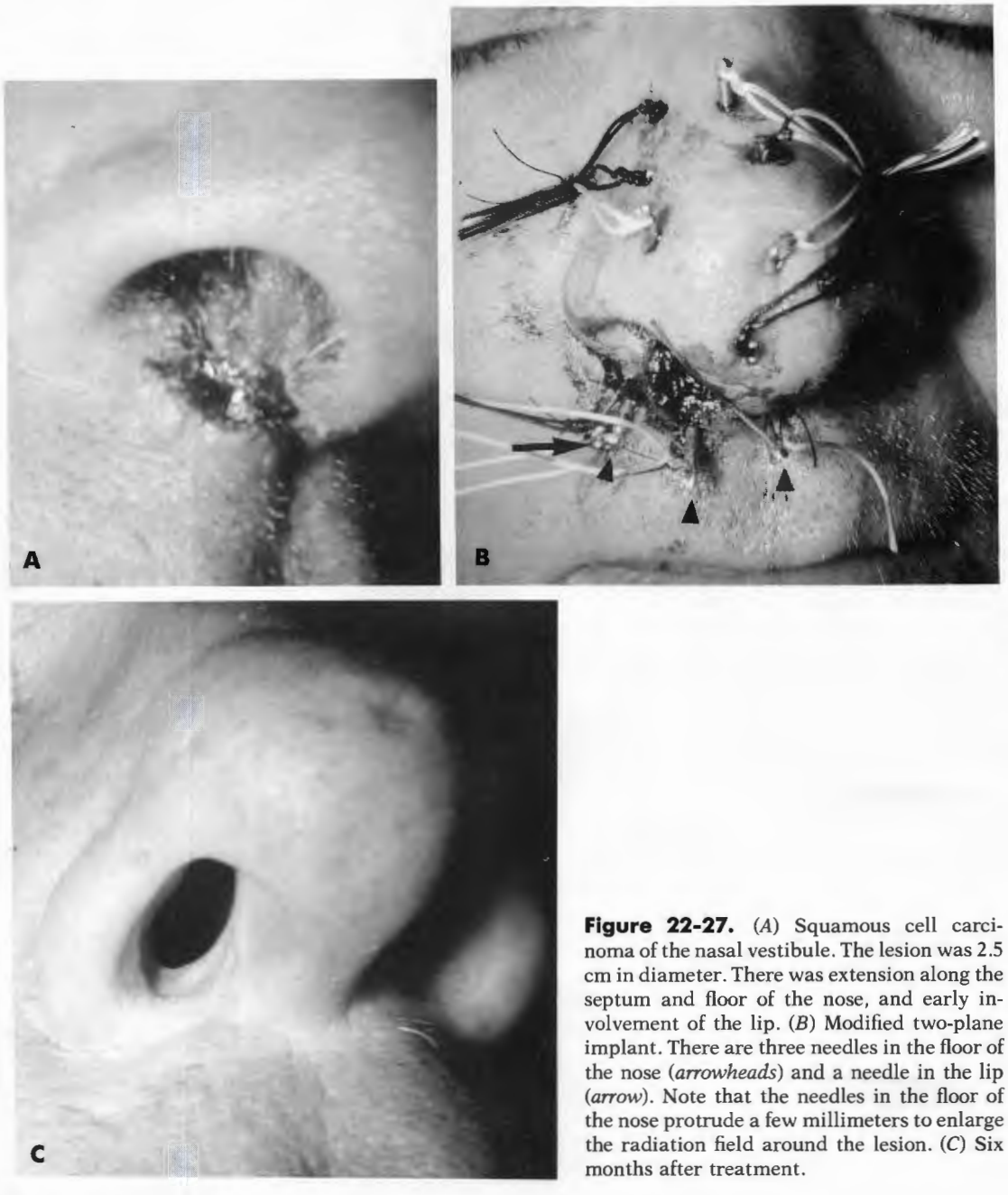


Figure 22-27. (*A*) Squamous cell carcinoma of the nasal vestibule. The lesion was 2.5 cm in diameter. There was extension along the septum and floor of the nose, and early involvement of the lip. (*B*) Modified two-plane implant. There are three needles in the floor of the nose (*arrowheads*) and a needle in the lip (*arrow*). Note that the needles in the floor of the nose protrude a few millimeters to enlarge the radiation field around the lesion. (*C*) Six months after treatment.

lateral or bilateral optic nerve injury. In most instances, current postoperative doses do not exceed 6000 to 6500 cGy (at 180 cGy per fraction once a day, or at 110 to 120 cGy twice a day), whereas the doses used in the past to treat moderate-volume gross disease, when irradiation was the sole treatment modality, were often about 7000 cGy minimum tumor dose. For patients with unresectable lesions, high-dose irradiation remains the only alternative; the current approach is to use 110 to 120 cGy twice a day with a 6-hour interfraction interval, in an attempt to reduce the risk of optic nerve injury. It is too early to tell if this approach will be successful.

The histologic features, extent, and location of malignant tumors of the nasal cavity and ethmoid sinus all are considered in making treatment decisions. Elective neck treatment generally is not prescribed except for recurrent or extensive, poorly differentiated tumors, particularly if areas rich in capillary lymphatics (eg, nasopharynx) are involved.

INVERTED PAPILLOMA. Inverted papilloma (without carcinoma) is treated initially by surgical excision. Limited excision by intranasal polypectomy, turbinectomy, ethmoidectomy, or anterior antrostomy has resulted in about a 70% rate of recurrence. Lateral rhinotomy and en bloc medial maxillectomy and ethmoidectomy, as well as removal of the middle and inferior turbinates and all mucosa in the ipsilateral paranasal sinuses, results in a 5% to 10% rate of recurrence.[52,67] An alternative surgical approach to lateral rhinotomy is

midfacial degloving, the major advantage of which is the absence of any external facial incision. When inverted papilloma begins to act aggressively with rapid recurrences and invasion of the sinuses, orbit, and cribriform plate, it should be considered a low-grade cancer and treated appropriately by more radical en bloc removal, irradiation, or both. Experience with irradiation is limited, but it is definitely of value.

Inverted papilloma associated with carcinoma is treated in the same fashion as other nasal carcinomas.

SQUAMOUS CELL CARCINOMA. Most early, discrete lesions of the nasal cavity are treated with surgery. Postoperative irradiation usually is added, except for small lesions of the septum.

At the University of Florida, the same general philosophy that is used for the treatment of cancers of the nasal cavity is applied to those of the ethmoid sinus. If the lesion is resectable, operation usually is performed first; postoperative irradiation (6000 to 6500 cGy at 180 cGy per fraction) is advised, even if the margins of resection are negative. En bloc removal requires craniofacial resection when the fovea ethmoidalis or cribriform plate are involved. If only a single modality of treatment is selected, irradiation produces a higher rate of cure than surgery alone. Patients with unresectable lesions are offered twice-a-day irradiation to a high dose.

MINOR SALIVARY GLAND CARCINOMAS. Low-grade tumors (such as low-grade adenocarcinoma, acinic cell carcinoma,[58] benign mixed tumor, low-grade mucoepidermoid carcinoma) of the nasal cavity are usually managed by surgical resection, without irradiation. Postoperative irradiation may be added if resection is incomplete, the lesion is extensive, or the lesion extensively involves the ethmoid air cells (especially if the orbital contents have been preserved). Postoperative irradiation is recommended for all high-grade tumors and all adenoid cystic carcinomas to widely treat the pathways of perineural extension (see Chap. 28).

ESTHESIONEUROBLASTOMA. Esthesioneuroblastoma is managed by craniofacial resection followed by postoperative irradiation. Unresectable disease usually is treated with high-dose irradiation alone.

No good evidence exists to suggest that adjunctive chemotherapy is of benefit in esthesioneuroblastoma. Spaulding and coworkers[73] reported on six patients with disease extending beyond the nasal cavity but still confined to the paranasal sinuses (stage B, one patient) or whose disease extended beyond the paranasal sinuses (stage C, five patients) who received adjunctive chemotherapy (intravenous vincristine and cyclophosphamide) followed by preoperative irradiation (5000 cGy) and craniofacial resection. Five of the six patients developed recurrent cancer. Compared with a group that did not receive chemotherapy, recurrences in the chemotherapy patients were, however, somewhat delayed. Schwaab and coworkers[66] used adjuvant chemotherapy consisting of vincristine, doxorubicin, dacarbazine, and cyclophosphamide in five patients after local treatment. Disease recurred in four patients. Eight additional patients received chemotherapy for distant metastases. No response, or temporary response, was observed in seven patients; in one patient chemotherapy apparently halted disease progression.

In a review of the literature on chemotherapy for advanced or metastatic esthesioneuroblastoma (13 patients), Wade and coworkers[78] noted several partial remissions and rare complete remissions that were of short duration (1 to 4 months); however, in one patient with extensive bone marrow metastases, the response was maintained at least 2 years postchemotherapy.[79]

MIDLINE GRANULOMA. Midline granuloma (polymorphic reticulosis) is treated by radiation therapy to the nasal cavity and all of the paranasal sinuses. Because marginal failure is common, the initial portals include the nasal cavity and all of the paranasal sinuses to 4000 cGy followed by additional treatment to boost the dose

Figure 22-28. (*A*) Squamous cell carcinoma of the columella, 1.5 × 1.5 cm, treated with a modified three-plane implant in the nasal vestibule plus two needles in the lip and two needles in the floor of the nose (6500 cGy over 6 days). (*B*) Appearance 1 year after treatment.

to the areas of gross disease to 5000 cGy (at 180 cGy per fraction).

SOFT TISSUE SARCOMAS. Surgical excision usually is the treatment of choice for sarcomas; preoperative or postoperative irradiation is added on an individual basis (see Chap. 33).

MALIGNANT MELANOMA. Primary nasal cavity melanomas are approached like squamous cell carcinomas. Resection is followed by postoperative irradiation. If the lesion is not resectable, high-dose irradiation is used. Although mucosal melanoma is commonly stated to be radioresistant, this has not been our observation. In three patients at the University of Florida, the tumor disappeared after conventionally fractionated treatment (180 to 200 cGy per day, 5 fractions per week). One patient remained free of disease for 8 years, after which distant metastases occurred; the other two developed local recurrences (one in-field, one geographic miss).

Surgical Treatment

The surgical approach and procedure for nasal cavity and ethmoid sinus tumors is determined by the extent of the lesion, as determined by physical examination and imaging studies. An en bloc resection of all involved bone and soft tissue with margins is the goal of any surgical technique. The approach is chosen to maximize exposure while preserving function and cosmesis.

The most common techniques employed for exposure are the lateral rhinotomy and the midface degloving procedures. The lateral rhinotomy employs an incision in the nasal–facial groove for access. It may be extended as a lip-splitting incision, or as an infraorbital incision (Weber-Fergusson). It provides direct exposure, but does require an external incision. The midface degloving procedure is accomplished through a sublabial incision from maxillary tuberosity to maxillary tuberosity combined with nasal intercartilaginous and transfixion incisions. The cosmetic result is excellent, but the exposure superiorly may be slightly limited.

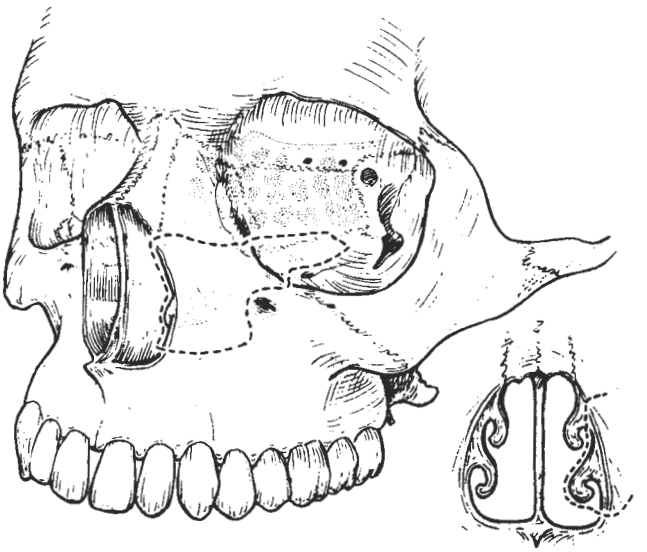


Figure 22-30. Inferior medial maxillectomy. (Weymuller EA Jr. Neoplasms. In: Cummings CW, Krause CJ, eds. Otolaryngology: head and neck surgery, vol. 1. St. Louis, CV Mosby, 1986:927)

Intranasal procedures are useful only for biopsy purposes, and are not adequate for any tumor resection.

An external en bloc ethmoidectomy (Fig. 22-29) is appropriate for few benign tumors. It is not, however, the procedure of choice for inverted papilloma, because it is associated with a high rate of recurrence. The medial wall of the orbit along with the ethmoid labyrinth is resected via an incision placed midway between the dorsum of the nose and the medial canthus.

Occasionally, a tumor may be limited to the inferior turbinate alone. In this situation, an inferior medial maxillectomy (Fig. 22-30) may be used. The bony resection includes the uncinate process, the inferior turbinate,

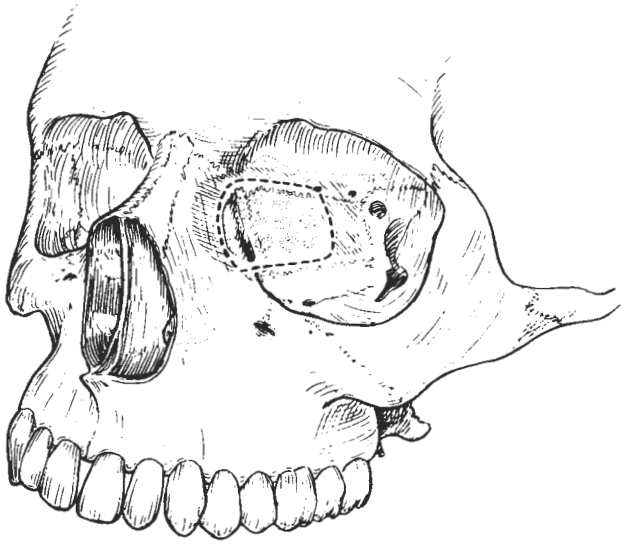


Figure 22-29. External ethmoidectomy. (Weymuller EA Jr. Neoplasms. In: Cummings CW, Krause CJ, eds. Otolaryngology: head and neck surgery, vol. 1. St. Louis, CV Mosby, 1986:927)

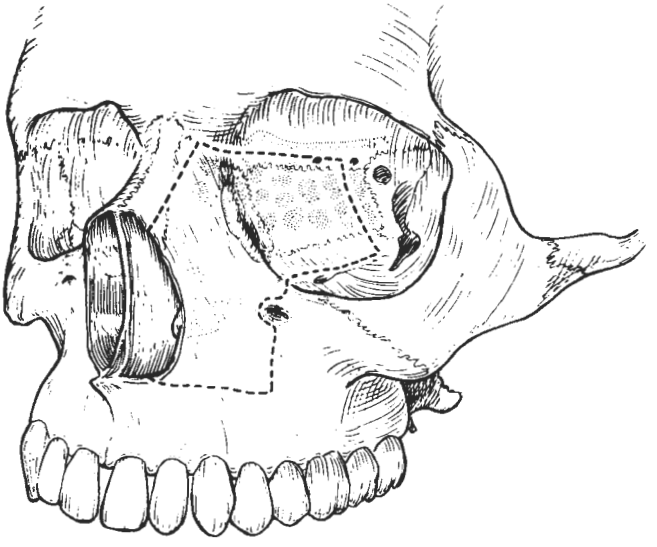


Figure 22-31. Medial maxillectomy. (Weymuller EA Jr. Neoplasms. In: Cummings CW, Krause CJ, eds. Otolaryngology: head and neck surgery, vol. 1. St. Louis, CV Mosby, 1986:927)

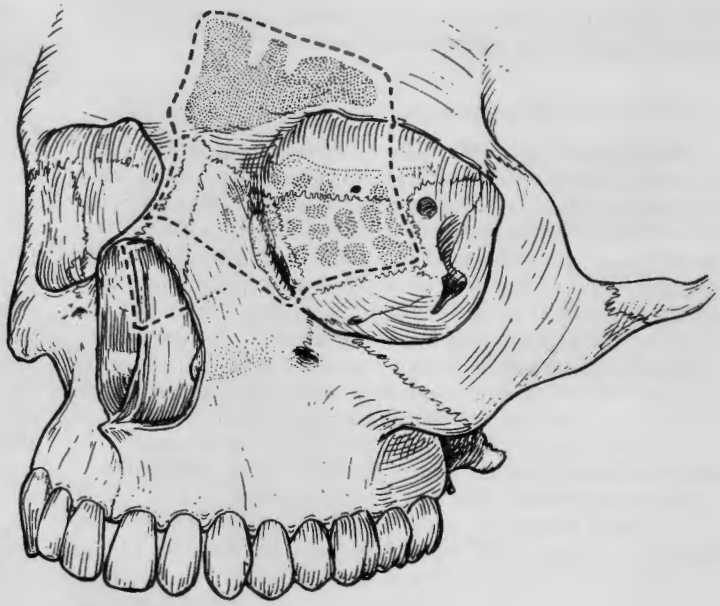


Figure 22-32. Craniofacial frontoethmoidectomy. (Weymuller EA Jr. Neoplasms. In: Cummings CW, Krause CJ, eds. Otolaryngology: head and neck surgery, vol. 1. St. Louis, CV Mosby, 1986:928)

and the inferior lateral nasal wall. Exposure may be achieved through either a lateral rhinotomy or a midface degloving approach.

The majority of ethmoid tumors are best extirpated with a medial maxillectomy and en bloc ethmoidectomy (Fig. 22-31). This should include the entire lateral nasal wall, the ethmoid labyrinth, the lamina papyracea, and the inferior and middle turbinates. Inverted papillomas are most appropriately managed in this fashion. This resection may be accomplished via lateral rhinotomy or midface degloving. Resection of all the turbinate tissue often is associated with nasal crusting postoperatively.

If the superior extent of tumor involves the fovea ethmoidalis or cribriform plate, then a combined craniofacial approach (craniofacial frontoethmoidectomy or extended craniofacial resection, Figs. 22-32 and 22-33) is required. A frontal craniotomy is used to resect the involved floor of the anterior cranial fossa. Dura may be removed if necessary. The resection may include the frontal sinus, ethmoid labyrinth, and the eye, if necessary. If the tumor crosses the midline, the procedure may be performed bilaterally. The resulting cranial floor defect should be closed with a vascularized pericranial or temporalis muscle flap. Larger defects may require the use of a revascularized distant muscle flap. Resection may be extended to include the cavernous sinus or sphenoid sinus; cure rates are dismal if the tumor involves these areas. Transdural tumor extension or optic chiasm involvement precludes complete resection.

No single definition for extended craniofacial resection exists. Each operation is individually tailored according to disease extent. The posterior line of resection is defined by the foramen ovale, foramen rotundum, and internal carotid artery. The excision may extend through the sphenoid sinus and up to the contralateral optic nerve. The remaining margins are those of the craniofacial frontoethmoidectomy and the radical maxillectomy. The operation does not provide adequate en bloc resec-

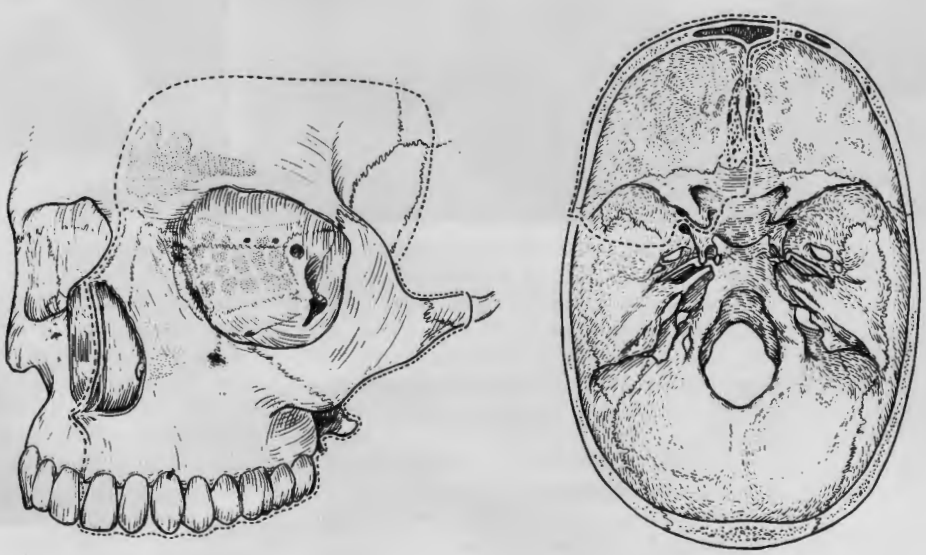


Figure 22-33. Craniofacial resection. (Weymuller EA Jr. Neoplasms. In: Cummings CW, Krause CJ, eds. Otolaryngology: head and neck surgery, vol. 1. St. Louis, CV Mosby, 1986:929)

tion for tumor in the orbital apex, nasopharynx, or deeply infiltrating the pterygoid space.[80]

Irradiation Technique

EXTERNAL BEAM. The external-beam techniques for nasal cavity, ethmoid sinus, and maxillary sinus cancers are similar. Treatment emphasizes an anterior portal with one or two posteriorly tilted lateral portals (frequently using wedges). Most commonly, treatment is administered with 6-MV or 8-MV x-rays. Even when the lesion is thought to be localized, we treat a large initial volume rather than relying too greatly on imaging and physical examination. Fields then are reduced to cover only the initial gross disease, with a margin, after 4500 to 5000 cGy. For limited cancers of the nasal cavity, the initial treatment volume includes the medial maxillary sinus, ethmoid sinus, medial portion of the orbit, nasopharynx, sphenoid sinus, and base of skull.[56]

Ethmoid sinus and advanced nasal cavity cancers are similarly managed (Figs. 22-34 and 22-35). The given doses (maximum dose [Dmax]) to the anterior and lateral fields are usually weighted 2 to 1 or 3 to 1 in favor of the anterior portal. The lateral portals typically do not encompass the entire volume of disease, because anterior tumor extensions cannot be treated via lateral portals without irradiating both eyeballs. Wedges are used to achieve a satisfactory dose distribution. A reduced anterior open field often is incorporated into the treatment plan to concentrate the dose to the major bulk of disease. Most ethmoid sinus tumors invade the orbit. When such invasion is minimal, the major lacrimal gland and lateral upper eyelid are shielded on the anterior portal; more advanced orbital invasion requires irradiation of the entire orbital contents (Fig. 22-36). An example of a two-field technique for advanced nasal cavity or ethmoid sinus cancers with invasion of the orbit is shown in Figure 22-37. If the ethmoid sinuses are extensively involved, but there is no clinical or radiographic evidence of orbital involvement, about one half to three quarters of the orbit is included to 4000 to 4500 cGy (180 cGy per fraction) to control possible microscopic disease extension (see Fig. 22-36*B*). Portals are then reduced to transect the ipsilateral eye just medial to the limbus (see Fig. 22-36*C*). This technique usually allows preservation of lacrimal and retinal function, but produces a cataract.

During treatment, patients are instructed to gaze straight ahead with the eyes wide open. The "lateral gaze" eye position was commonly used at the University of Florida until 1970; the technique was discontinued

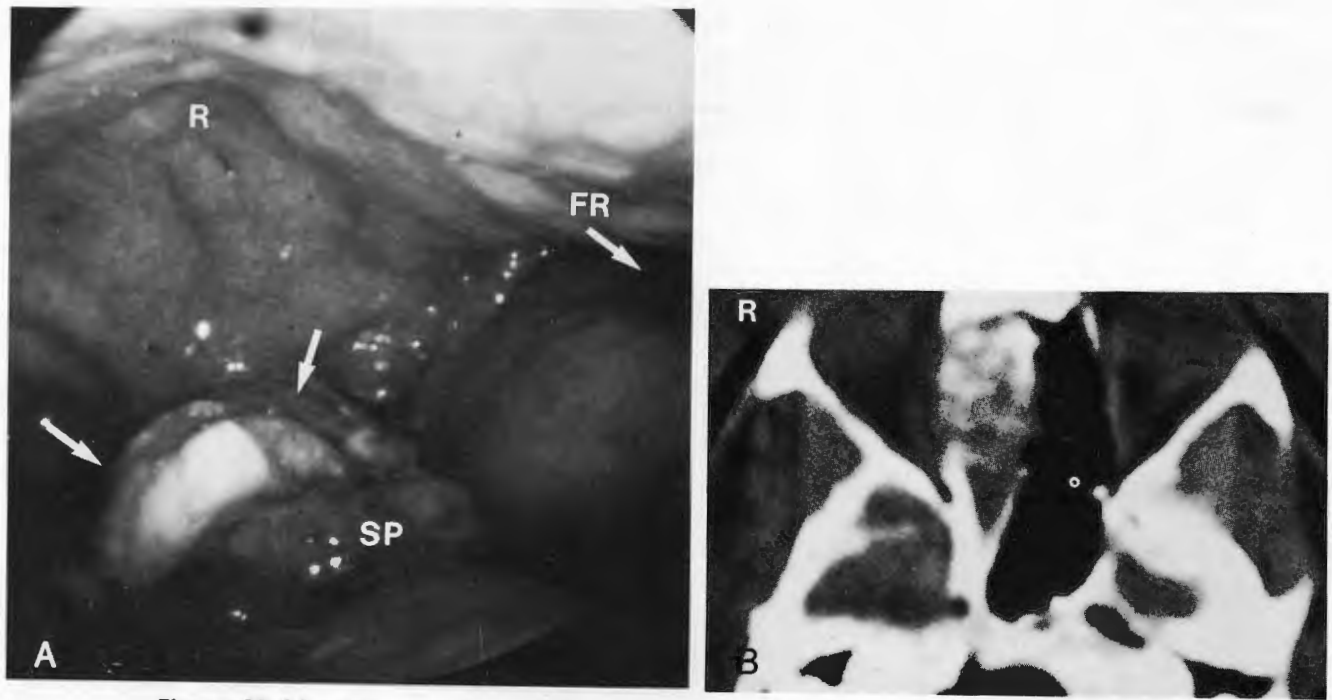


Figure 22-34. A 33-year-old man had a 1-year history of left nasal congestion and frontal headaches, a 6-month history of epistaxis, and a 3-month history of tearing of the left eye. There was a granular lesion filling the entire nasal cavity and extending into the nasopharynx. Biopsy showed squamous cell carcinoma. (*A*) Tumor mass extending into nasopharynx (*arrows*). Roof (R), soft palate (SP), and right fossa of Rosenmüller (FR). (*B*) CT at the level of the orbit and ethmoids. There is opacification of the right ethmoid sinus and nasal cavity. The mass bulges into the medial aspect of the left orbit. Additional views showed opacification of the left sphenoid and maxillary sinuses, erosion of left pterygoid plates, and possible erosion of the cribriform plate. Diagnosis was squamous cell carcinoma of the ethmoid sinus with invasion of the maxillary sinus, sphenoid sinus, nasal cavity, and nasopharynx. The site of origin was an educated guess, and could have been the nasal cavity or upper medial maxillary antrum. The tumor was thought to be unresectable because of involvement of the nasopharynx and possible sphenoid sinus invasion.

because it rotated the posterior pole (and retina) into the treatment portal. An eyelid retractor is used to displace some of the upper lateral lid from the treatment field. Narrow margins around the eye commonly result in treatment failure. The anterior portal extends 1.5 to 2.0 cm across the midline to encompass the entire nasal cavity and ethmoid–sphenoid complex, and the medial aspect of the contralateral orbit. The superior margin encompasses the cribriform plate and includes all or part of the frontal sinus. The inferior margin (at or near the lip commissure) encompasses the floor of nose, maxillary antrum, and alveolar ridge; the tongue is displaced by a tongue blade and cork from the treatment field.[20,50,56]

For lesions of the nasal cavity without orbital or extensive ethmoid sinus invasion, the field edge is placed at the ipsilateral medial limbus. If gross disease exists in the ethmoid sinuses, field reductions should be made with great caution, because of both the high incidence of subclinical tumor extension through the lamina papyracea, and the anatomic configuration of the sinus. Al-

Figure 22-35. Treatment techniques for the patient in Figure 22-34. (*A*) Simulation film of the anterior portal. The straight white line is the aluminum support for the bite block. (*B*) Radiation therapy treatment portals were anterior and left and right laterals. The upper lateral eyelid and the lacrimal gland were shielded because only the medial orbit was involved by tumor. (*C*) Simulation film of the lateral portal (5-degree posterior tilt). The portal encompasses the base of the skull, posterior ethmoid and maxillary sinuses, posterior nasal cavity, sphenoid sinus, nasopharynx, posterior one third of both orbits, pterygoid plates, infratemporal fossa, and the parapharyngeal lymph nodes. The posterior border is just anterior to the external auditory canal, thereby excluding the cervical spinal cord and brain stem. (*D*) The treatment plan was 7000 cGy minimum (7700 cGy maximum) tumor dose in 7 weeks. The given doses were weighted 2 to 1 in favor of the anterior portal. The right and left upper neck received 4050 cGy in 3 weeks through an anterior portal with midline shielding. The visible tumor disappeared during therapy. The patient returned to full-time work as a truck driver at 4 months. A cataract developed in the left eye at 36 months; after cataract extraction, visual acuity was only "counts fingers at 2 feet" because of radiation retinopathy. The patient was free of disease at 14 years. (*A* and *C* from Ellingwood KE, Million RR. Cancer of the nasal cavity and ethmoid/sphenoid sinuses. Cancer 1979;43:1520, 1521. *D* from Parsons JT, Million RR. Cancer of the nasal cavity and paranasal sinuses. In: Perez CA, Brady LW, eds. Principles and practice of radiation oncology. Philadelphia, JB Lippincott, 1987:507)

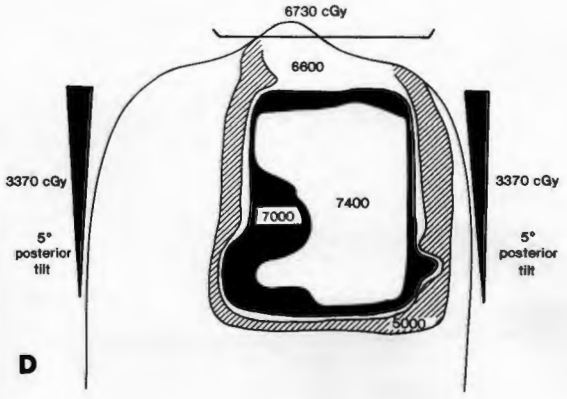


Figure 22-35. ***(Continued)***

though the lateral walls of the ethmoid sinuses are parallel in their upper portions, inferiorly and posteriorly they diverge, conforming to the cone-shaped orbit. If the eyeball is totally shielded from the anterior portal, some posteroinferior ethmoid air cells also will be shielded. The same principle applies to the roof of the maxillary sinus, which slopes upward as it proceeds from anterior to posterior. In some patients, the anterior portal is tilted cephalad (eg, 10 to 12 degrees) so that the beam parallels the inferomedial and inferior orbital walls, allowing more adequate treatment of the sinuses while irradiating less of the orbit.

The anterior border of the lateral portals (see Figs. 22-35 and 22-36*D*) is frequently at the lateral bony canthus. The posterior pole of the ipsilateral eyeball is within the lateral fields; the contralateral globe is missed because the portals are angled 5 degrees posteriorly. The superior border of the lateral field is adjusted according to disease extent. It is generally 1 cm above the roof of the ethmoid sinuses, but may be raised 2 to 3 cm to treat intracranial extension. The inferior border usually is at the level of the lip commissure. A cork and a tongue blade displace the tongue from the field. The posterior border and the posterosuperior borders exclude the spinal cord and brain stem, respectively. The posterior border usually is at or near the tragus and bisects the vertebral bodies. The posterosuperior border usually is 2 to 3 mm behind the clivus. If the spinal cord and brain stem are included within the lateral portals for the initial 5000 cGy, the total dose to these structures at the completion of treatment (assuming that treatment is continued to 6000 or 7000 cGy) will exceed 5000 cGy because, even though the structures can be excluded from the lateral portals, they will be included within the reduced anterior portal. The brain stem and spinal cord are included within the lateral portals only in the rare circumstance of tumor extension posterior to the plane of the cord. In this setting, patients must be apprised of the increased risk of neurologic sequelae.

High-energy electrons should be used with caution in the central face region. Because of the inhomogeneity of patients' contours and the presence of air cavities in this region, there will be so-called "hot spots" lateral to the nose. If the electron energies are high, these areas of relative overdosage may extend deep enough to encompass the optic nerves.[51]

Combined Treatment Policies

If combined treatment is planned, we prefer to operate first to avoid obscuring the extent of tumor and to limit the risk of operative and postoperative complications. Radiation therapy is started 4 to 6 weeks afterward.

Diagnosis and Management of Recurrence

Recurrent disease is heralded by recurrent pain and cranial nerve palsies. Exploration of the sinuses may be necessary for diagnosis. After an operation or radiotherapy, it is difficult to determine the extent of recurrent disease by CT or MRI, because of changes from the previous therapy. Baseline CT or MRI about 3 months after treatment is helpful. MRI may be better than CT at distinguishing between fibrosis and recurrent tumor. Granulation tissue cannot be distinguished from tumor unless there has been progressive growth. The most common situation requiring salvage treatment is a radiation or surgical failure that can be treated successfully by craniofacial resection. Radiation therapy should be used post-

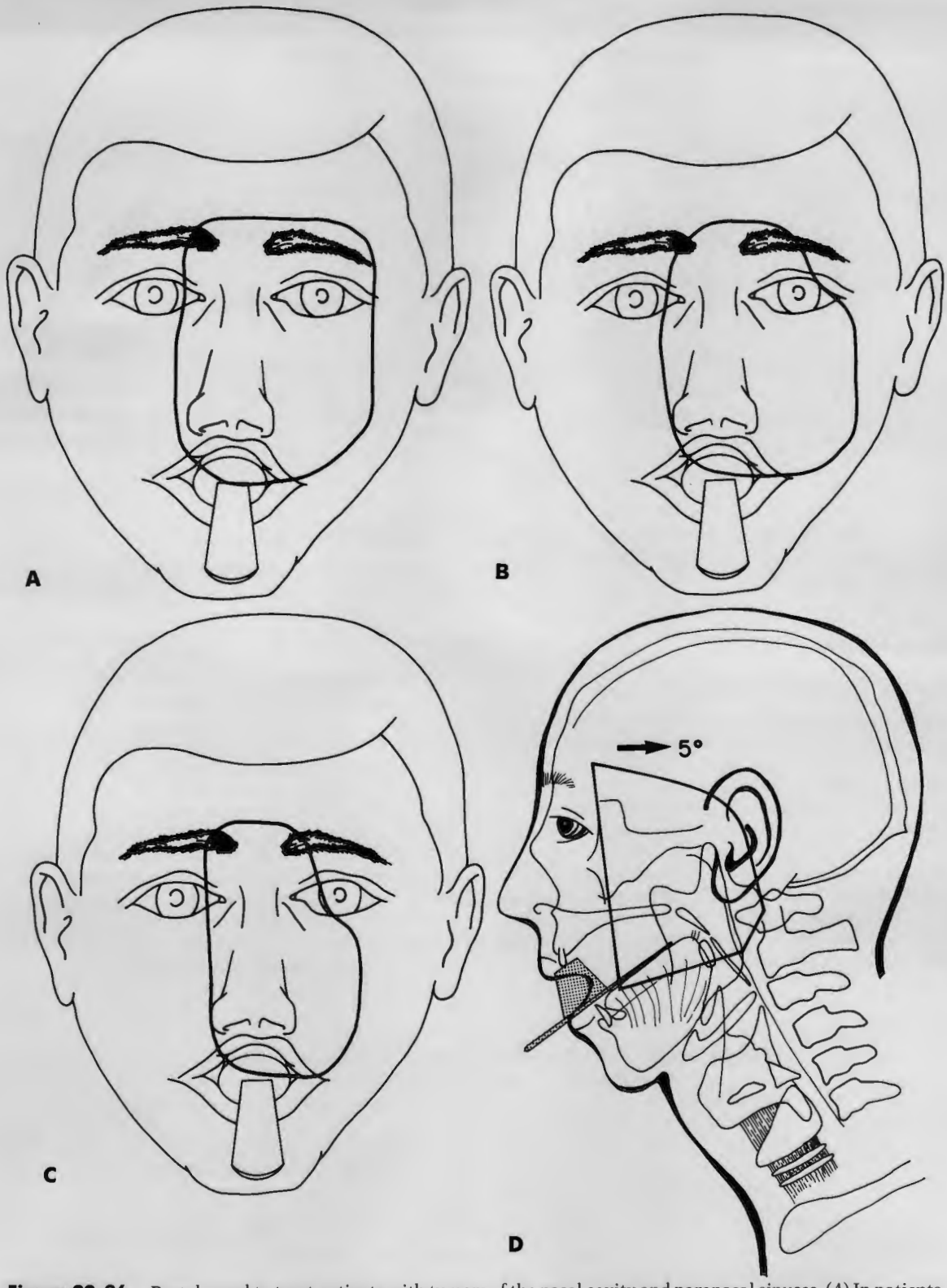


Figure 22-36. Portals used to treat patients with tumors of the nasal cavity and paranasal sinuses. (*A*) In patients with extensive orbital invasion (eg, palpable orbital mass, proptosis, or blindness), all of the orbital contents are irradiated. (*B*) In patients with limited orbital invasion, the major lacrimal gland is shielded. (*C*) Portal primarily used for patients with limited lesions of the nasal cavity, or as a reduced field for an ethmoid sinus primary lesion. (*D*) Typical lateral portal for treatment of tumors of the paranasal sinuses and nasal cavity. The field is angled 5 degrees posteriorly to avoid exit irradiation to the contralateral eye. Special attention should be paid to the dose to the brain stem and spinal cord, including the contribution from the anterior portal. Further technical details are described in the text. (*A* through *C* from Parsons JT, Mendenhall WM, Bova FJ, Million RR. Head and neck cancer. In: Levitt SH, Khan FM, Potish RA, eds. Levitt and Tapley's technological basis of radiation therapy: practical clinical applications, ed 2. Philadelphia, Lea & Febiger, 1992:225. *D* from Parsons JT, Million RR. Cancer of the nasal and paranasal sinuses. In: Perez CA, Brady LW, eds. Principles and practice of radiation oncology. Philadelphia, JB Lippincott, 1987:509)

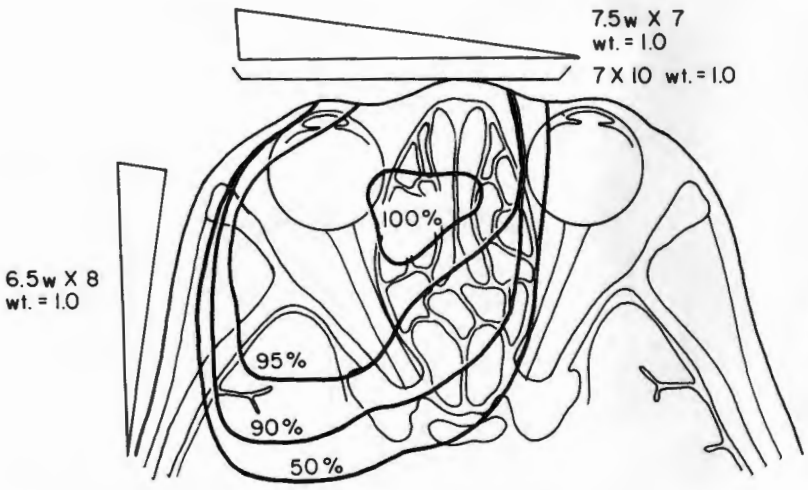


Figure 22-37. Isodose distribution for carcinoma of the ethmoid sinus with invasion of the orbit. The lateral portal is angled 5 degrees posteriorly. (Million RR, Cassisi NJ, Wittes RE: Cancer in the head and neck. In: DeVita VT Jr, Hellman S, Rosenberg SA, eds: Cancer: principles and practice of oncology, ed 3. Philadelphia, JB Lippincott, 1989:566)

operatively (if it has not been previously used) even if the margins are negative. About 25% of patients may be salvaged with this approach.

Maxillary Sinus

Selection of Treatment Modality

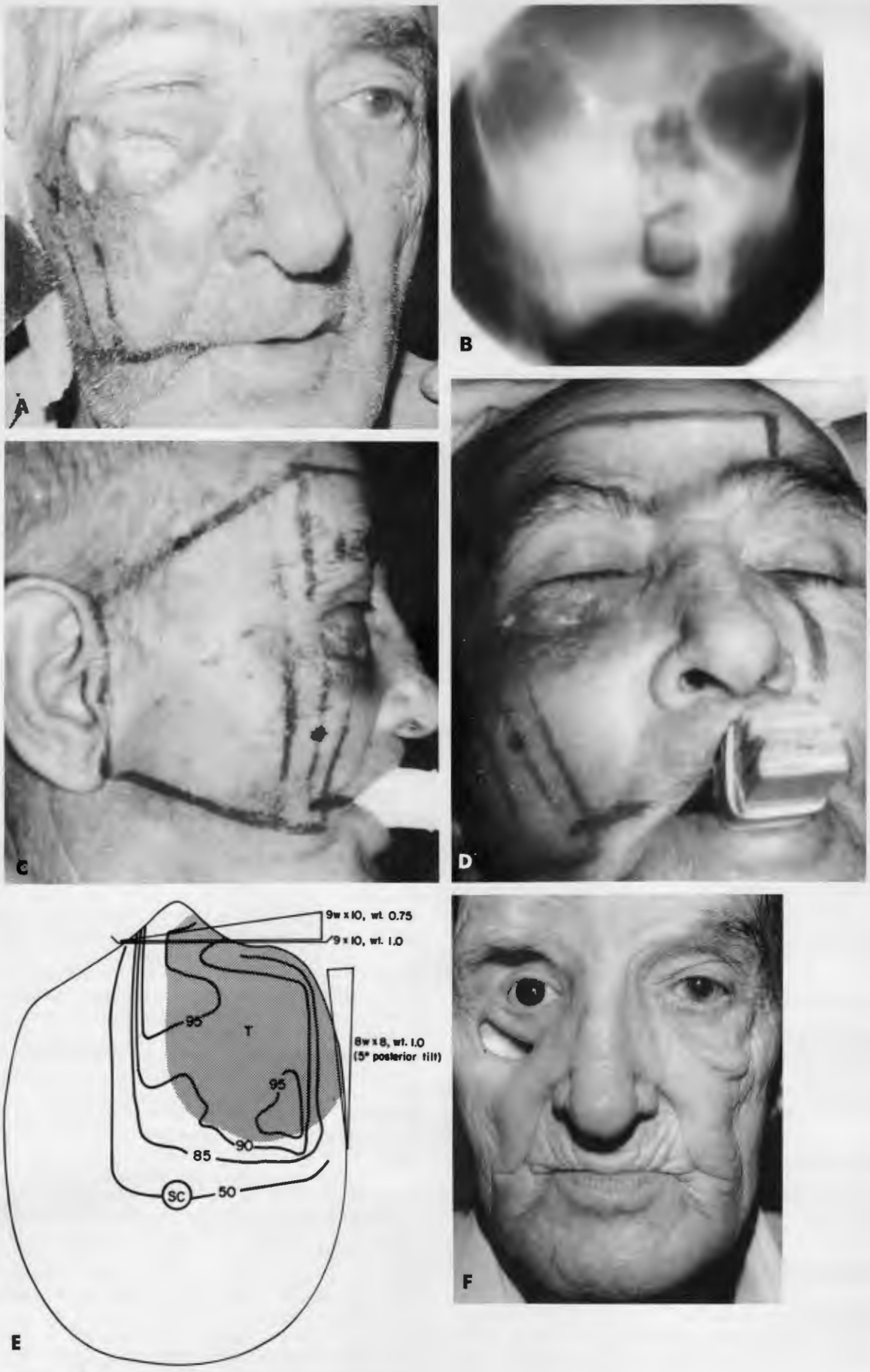
Surgical resection gives the best results. Early infrastructure lesions are often cured by surgery alone, but in most cases of maxillary sinus cancer, irradiation is given postoperatively, even if the margins are clear. Massive tumor extension to the base of the skull, nasopharynx, or sphenoid sinus usually contraindicates surgery. Borderline resectable lesions sometimes are treated with full-dose, external-beam irradiation, followed by operation if technically feasible. Many patients refuse operation because of the defect imposed by maxillectomy and possible orbital exenteration. Radiation therapy alone cures about 10% to 15% of advanced cases (Fig. 22-38).

Surgical Treatment

The majority of maxillary malignancies require radical maxillectomy (Fig. 22-39) including the entire maxilla and ethmoid sinus via a Weber-Fergusson incision. The globe and orbital floor may be preserved for inferiorly located tumors. Tumor extension outside of the antrum dictates additional margins of resection. Orbital exenteration is included when tumor has spread into the periorbita. The procedure may be further extended to include the pterygoid plates, pterygoid musculature, the mandibular condyle, the coronoid process, or facial muscles as required. In cases where tumor involves the ethmoid roof, craniofacial resection is required.

A split-thickness skin graft is placed to promote epithelialization of the cavity. The cavity is temporarily filled with packing, supported by a preformed dental prosthesis. Once healing is complete, a permanent prosthesis is used to fill the palatal defect. An orbital prosthesis may be constructed as well.

Figure 22-38. A 71-year-old man with a long history of sinusitis, treated by polypectomy and bilateral ethmoidectomies. Two months before admission, he noticed pain in the right cheek and a mass below the right lateral eyelid. The mass spontaneously drained through the skin. There was recent onset of diplopia. (*A*) Pus was draining from the right cheek mass, the lids were red and edematous, and there was proptosis of the right eye. The orbit was filled with a rock-hard mass. The nasal cavity was occluded by tumor, but the nasopharynx was normal (T4N0). Biopsy revealed squamous cell carcinoma. (*B*) Tomography showed an opacified right maxillary antrum, right ethmoid and sphenoid sinuses, and right nasal cavity with destruction of the medial and inferior orbital walls. There was no intracranial extension. CT confirmed the above. The patient refused any form of operation and received radiation treatment using ^{60}Co. (*C*) The right lateral portal. (*D*) The anterior portal. A stack of tongue blades was used to depress the tongue out of irradiation portals. Anterior and lateral portals overlapped approximately 2 cm on the skin surface. (*E*) The minimum tumor dose was 7000 cGy in 40 fractions, specified at 85% of maximum isodose line, administered by continuous-course irradiation. There was complete regression of obvious tumor at 5000 cGy. Diplopia disappeared, and vision returned to normal. Pneumatic equalization tubes were inserted for bilateral serous otitis media. Blurry vision developed at 14 months due to superficial keratitis secondary to dry eye and a cataract. The right cornea perforated spontaneously at 22 months and was repaired with a corneal transplant. The transplant failed, and the right eye was enucleated. (*F*) At 5 years, an artificial eye was inserted, but caused intermittent discomfort. The antrocutaneous fistula persisted, but was asymptomatic and provided a porthole for antrum examination. No evidence of disease existed at 11 years. (*E* from Parsons JT, Million RR. Cancer of the nasal cavity and paranasal sinuses. In: Perez CA, Brady LW, eds. Principles and practice of radiation oncology. Philadelphia, JB Lippincott, 1987:502)


A
B
C
D
9w x 10, wt. 0.75
9 x 10, wt. 1.0
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(5° posterior tilt)
95
T
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Figure 22-38.

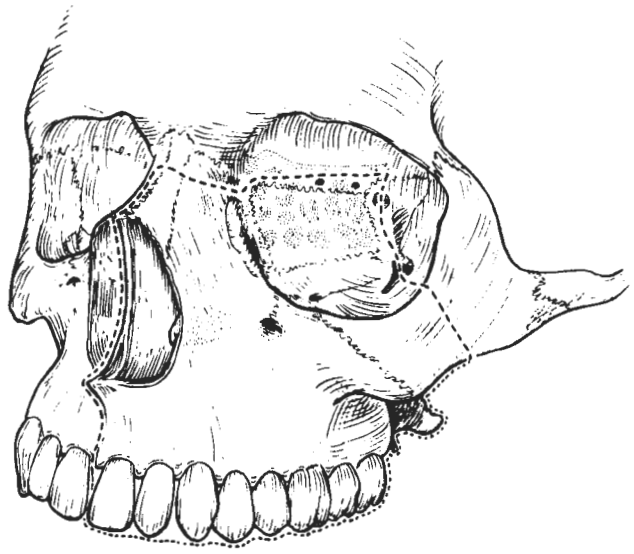

Figure 22-39. Radical maxillectomy. (Weymuller EA Jr. Neoplasms. In: Cummings CW, Krause CJ, eds. Otolaryngectomy: head and neck surgery, vol. 1. St. Louis, CV Mosby, 1986:927)

Irradiation Technique

The irradiation treatment volume includes the entire maxilla, adjacent nasal cavity, ethmoid sinus, nasopharynx, and pterygopalatine fossa, and at least a portion of the adjacent orbit. The entire orbit is included in patients with major extension into the orbital fossa; failure to include the orbital contents is a common cause of failure.

The anterior and lateral portals for maxillary sinus cancers resemble those for nasal cavity and ethmoid sinus lesions. The inferior border must encompass tumor in the gingivobuccal sulcus, buccal mucosa, low parapharyngeal, or tonsillar regions. If the temporal fossa is grossly invaded, the lateral border of the anterior portal is allowed to fall off.[55]

Drainage procedures are performed, if needed, before, during, or after radiation therapy.

Combined Treatment Policies

Except for early infrastructure lesions, surgical resection is followed in 4 weeks by external-beam irradiation. The dose usually is 6000 to 6500 cGy (at 110 cGy twice a day or 180 cGy once a day). Higher doses are recommended for gross residual disease.

Management of Recurrence

Recurrence after radiation therapy or surgery is sometimes resectable by craniofacial resection.

Sphenoidal Sinus

Treatment planning is similar to that for advanced carcinoma of the nasopharynx. The most common arrangement uses lateral fields alone. If significant anterior extension between the eyes exists, treatment emphasizes a cephalically-tilted anterior portal.

RESULTS OF TREATMENT

Nasal Vestibule

The results for nasal vestibule carcinoma often are included under nasal cavity results, and may give a falsely high rate of success for nasal cavity treatment.

McNeese and coworkers[47] reported on 32 previously untreated patients with squamous cell carcinoma of the nasal vestibule, who received radiation therapy alone at the M.D. Anderson Hospital between 1967 and 1984. All patients had neck nodes that were clinically negative for disease. In 11 patients with small, well-localized lesions, the disease was controlled by interstitial radium or iridium implants. In 20 of 21 patients treated with external-beam irradiation (electrons or electrons plus photons), the disease was locally controlled. Fourteen patients received elective neck irradiation to the upper neck plus or minus the facial nodes; none developed nodal failure. Four of 18 patients who received no elective nodal irradiation developed neck node recurrences; two were successfully salvaged. One significant complication occurred (maxillary osteoradionecrosis).

Between October 1964 and February 1988, 39 patients with squamous cell carcinoma of the nasal vestibule received radical radiation therapy with curative intent at the University of Florida.[46] The primary lesions were previously untreated in 29 patients and were recurrent after surgery in the other 10. All patients (including those whose tumors were recurrent after surgery) were staged by the 1988 AJCC classification for skin cancer according to tumor extent at the start of radiation therapy. Two patients presented with clinically positive lymph nodes. The rates of local control are given according to T stage in Table 22-3 and according to treatment technique in Table 22-4. The control rates were the same in patients whose tumors were recurrent after surgery as in previously untreated patients. Some small-volume lesions were classified as T4 on the basis of extension into or through cartilage; others in the T4 category had massive lesions that destroyed nasal soft tissue and bone (premaxilla). For T4 cancers, control correlated best with lesion size (11 of 13, or 85% for tumors less than 4 cm; and 1 of 4 for tumors 4 cm or larger in size). The results for 37 patients who were clinically negative for disease in the neck are shown in Table 22-5. Fifteen percent of patients whose necks received no elective treatment developed lymph node metastases; all have been successfully salvaged by neck dissection, and none has died of cancer.

Complications have been infrequent, and cosmesis generally has been excellent, unless patients had a prior operation. Four patients developed transient soft tissue necroses. One patient developed squamous cell carcinoma of the skin, located in the treatment field, 19 years after radiation therapy.

The 5-year absolute survival rates were 77% for stages I and II, and 73% for stages III and IV.

Wong and coworkers[81] reported on 56 patients who underwent primary external irradiation for squamous cell carcinoma of the nasal vestibule at the Princess Margaret Hospital (Toronto) between 1958 and 1983. The 5-year relapse-free local control rate for 34 patients with tumors less than 2 cm in size was 97%, versus 57% for those with larger tumors. Patients whose tumors extended to cartilage, bone, the upper lip, the skin of the nasal ala, and the columella also had a lower rate of local control (68%) than those without such extension (90%).

TABLE 22-3. Squamous Cell Carcinoma of the Nasal Vestibule: Local Control After Radiation Therapy (University of Florida, 39 Patients)

1988 AJCC Stage	No. Patients	Excluded*	Control With Initial Therapy	Control Including Salvage
TX–1	13	0	11/13	12/13
T2	8	2	6/6	6/6
Total TX–2			17/19 (89%)	
T3	—	—	—	—
T4	18	1	12/17 (71%)	15/17 (88%)

AJCC: American Joint Committee on Cancer.

* Dead of neck recurrence, distant metastasis, or intercurrent disease at <2 y with primary continuously controlled.

(Modified from McCollough WM, Mendenhall NP, Parsons JT, Mendenhall WM, Stringer SP, Cassisi NJ, Million RR. Radiotherapy alone for squamous cell carcinoma of the nasal vestibule: management of the primary site and regional lymphatics. Int J Radiat Oncol Biol Phys 1993;26:75)

TABLE 22-4. Squamous Cell Carcinoma of the Nasal Vestibule: Local Control After Radiation Therapy According to Irradiation Technique (University of Florida)

T Stage	External Beam Alone	Interstitial Implant Alone	External Beam Plus Implant
TX–1	2/3	6/6	3/4
T2	1/1	2/2	3/3
T3	—	—	—
T4	5/7	1/1	6/9

(Modified from McCollough WM, Mendenhall NP, Parsons JT, Mendenholl WM, Stringer SP, Cossisi NJ, Million RR. Radiotherapy alone for squamous cell carcinoma of the nasal vestibule: monagement of the primary site and regional lymphatics. Int J Radiat Oncol Phys 1993;26:75)

TABLE 22-5. Squamous Cell Carcinoma of the Nasal Vestibule: Management of Patients With Stage N0 Neck (University of Florida, 37 Patients)

Neck Treatment	No. of Patients	Excluded*	Control With Initial Therapy	Control Including Salvage
No elective treatment	32	5	23/27 (85%)	27†/27 (100%)
Elective radiation therapy (all T4)	5	2	3/3	3/3

* Excluding three patients who died of intercurrent disease at <2 y and four patients with local recurrence and neck controlled.

† One potient hos had <1 y of follow-up since surgery.

(McCollough WM, Mendenhall NP, Parsons JT, Mendenhall WM, Stringer SP, Cassisi NJ, Million RR. Radiotherapy alone for squamous cell carcinoma of the nasal vestibule: management of the primary site and regional lymphatics. Int J Radiat Oncol Biol Phys 1993;26:75)

When higher doses were given, the adverse effects of size and tumor extension were partially overcome (Table 22-6). Mak and coworkers[40] noted almost identical effects of dose and lesion size on the local control rate in 47 patients who received external irradiation at the Rotterdam Radiotherapy Institute (in The Netherlands).

The highest rates of local control have been obtained in lesions that have been treated by interstitial implant alone: 26 of 27 T1–2 lesions treated with iridium at the Institut Gustave Roussy (Villejuif, France),[14] 9 of 9 cancers treated with radium at the University of Florida, 11 of 11 cancers treated with iridium or radium at the M. D. Anderson Hospital (Houston),[47] and 21 of 22 cancers treated by interstitial iridium in Rotterdam.[8] These high rates of control are, no doubt, partly a reflection of the selection of early tumors for treatment by implant alone.

TABLE 22-6. Nasal Vestibule Cancer: Five-Year Local Control According to Tumor Size, Extent, and Dose After External-Beam Irradiation (Princess Margaret Hospital, 1958–1983)

	Tumor Dose	
Tumor Size	<5500 cGy/5 wk	≥5500 cGy/5 wk
<2 cm	11* (100%)†	22 (95%)
≥2 cm	11 (30%)	11 (82%)
Extension to cartilage, bone, lip, ala, columella		
No	7 (86%)	20 (95%)
Yes	15 (51%)	13 (85%)

* No. patients in category.

† Percentage of patients whose tumors were controlled locally at 5 y. (Modified from Wong CS, Cummings BJ, Elhakim T, Briant TD. External irradiation for squamous cell carcinoma of the nasal vestibule. Int J Radiat Oncol Biol Phys 1986;12:1945)

Nasal Cavity and Ethmoid Sinus

Inverted Papilloma

Recurrence after radical excision (usually lateral rhinotomy with en bloc excision of the lateral nasal wall) is uncommon (5% to 10%).[35,52,67] Recurrences usually manifest themselves within 2 years, but on rare occasions are delayed for greater than 10 years.[35]

Myers and coworkers[52] treated six patients with concurrent squamous cell cancer with curative intent by combined irradiation and surgery. Four of six remained free of disease at 10 to 13 years.

Experience with radiation therapy is limited. Between December 1969 and March 1985, seven patients with advanced, biologically aggressive, inverted or cylindrical cell papillomas were treated with irradiation at the University of Florida.[25] One patient had associated squamous cell carcinoma in situ and one patient had invasive squamous cell carcinoma.

Three patients were treated with radiation therapy alone (6500 cGy in 36 to 37 fractions) because of medical inoperability (one patient) or advanced, unresectable, recurrent local disease (two patients). One patient with an advanced, recurrent tumor developed a local recurrence extending into the frontal lobe of the brain and died 17 months after radiation therapy. The other two had no evidence of recurrence at 7 and 8 years, respectively.

Three patients received postoperative irradiation (4700, 6100, and 6500 cGy, respectively) for gross residual cancer (two patients) or microscopic residual disease (one patient). No recurrences were observed at 4.5, 9, and 20 years, respectively.

One patient received preoperative irradiation (6920 cGy, 120 cGy twice a day) for an extensive tumor. The surgical specimen contained no tumor, and the patient remains disease-free at 8 years.

No patient experienced a significant complication of radiation therapy. Although surgery generally is the primary treatment for this disease, radiation therapy should be considered for advanced, multiply recurrent, incompletely resected, or unresectable lesions.

Minor Salivary Gland Carcinomas

ADENOCARCINOMA. Klintenberg and coworkers[33] reported on 28 patients with adenocarcinoma of the ethmoid sinus. Most were men who worked with hardwoods in the furniture industry. The usual treatment was preoperative irradiation and surgery. One third of patients who received preoperative irradiation had no tumor remaining at operation; none of the group who responded with complete tumor disappearance developed recurrent disease. The 5-year survival rate was 55%. No patient developed lymph node metastases.

Heffner and coworkers[28] reviewed 50 cases of adenocarcinoma of the nasal cavity or ethmoid sinus from the Armed Forces Institute of Pathology. Prognostically, patients were divided into two groups: low-grade adenocarcinoma (23 patients), and high-grade adenocarcinoma (27 patients). The gender distribution of the low-grade group was about equal, whereas in the high-grade group there was a predominance of men.

Sixteen (70%) of the 23 patients with low-grade lesions remained continuously disease-free at 3.5 to 11 years after treatment, which most often consisted of surgery alone (19 patients) or surgery and postoperative irradiation (4 patients). Times to recurrence were 6 months, 8 months, 9 months, 3 years, 3 years, 4 years, and 6 years (average, 2.6 years). Limited surgical procedures (excisional biopsy or polypectomy) most often resulted in local recurrence, and predisposed patients to multiple further recurrences or unresectable extension. Only one patient, who had an extensive local recurrence, developed distant metastases; no lymph node metastases occurred. The value of radiation therapy could not be assessed, but apparently it was not necessary if a major cancer operation resulted in complete excision, since the results were almost uniformly good in this circumstance.

In comparison with patients with low-grade tumors, the prognosis in the high-grade group was poor. Seventy-eight percent died of disease, with almost 90% of the deaths occurring within 3 years. Only 7% (2 of 27 patients) remained continuously disease-free after treatment. Two thirds of patients received postoperative irradiation, most often after extensive surgery.[28]

BENIGN MIXED. Benign mixed tumors of the nasal cavity have a high rate of control after surgical resection alone.

Squamous Cell Carcinoma

Frazell and Lewis[22] reported a 5-year cure rate of 56% for 68 nasal cavity cancers treated surgically, versus 18% in 28 patients who were treated by irradiation. Eighty percent of the cancers were squamous cell carcinomas. Criteria for selection of treatment and stage were not analyzed. For patients with ethmoid sinus cancers, the authors reported 5-year cure rates of 40% for radiation therapy and 19% for operation; they concluded, however, that operation was the treatment of choice.

Bosch and associates[12] reported a 5-year survival rate of 56% for patients with nasal cavity cancer; 85% were treated by radiation therapy alone. About 80% of the cancers were squamous cell carcinoma. Their series included an unspecified number of nasal vestibule lesions. The series by Hawkins and coworkers[27] reported a 52% 5-year survival rate, but also included some cancers of the nasal vestibule.

Boone and coworkers[11] reported the M. D. Anderson Hospital experience for 28 patients with nasal cavity carcinoma. The 5-year absolute cure rate was 63%, and the local recurrence rate was 21%.

Esthesioneuroblastoma

After surgery alone for esthesioneuroblastoma, the 5-year survival rate is about 50%; the continuous disease-free survival rate is much lower.[54,68] Olsen and DeSanto[54] reported that only 4 (21%) of 19 patients from the Mayo Clinic (Rochester, MN) remained continuously free of disease 5 years after resection; Shah and Feghali[68] noted 5-year continuous disease-free survival in only 2 (6%) of 31 patients from Memorial Sloan-Kettering (New York). Twenty-three of the 31 patients required two or more surgical resections, and some patients required as many as 10 to 17 operations. In both the Memorial and Mayo Clinic series, patients tended to have a series of increasingly grave local recurrences, which predisposed them to the development of unresectable intracranial extension, lymph node metastasis, and distant metastasis. At least half of all recurrences, in some series, could not be salvaged by secondary treatment.[6,54] Late failures (5 to 10 or more years after treatment) are not rare.[6,54,68] Eventual development of distant metastases (usually osseous or pulmonary) is noted in 25% to 30% of patients.[54,66] In a literature review by Elkon and coworkers[19] in 1979, local recurrence accounted for almost 70% of observed treatment failures. The authors concluded that single-modality treatment (radiation therapy or surgery) is just as effective as combined-modality treatment in early-stage disease because some failures can be salvaged, but the lowest recurrence rates were noted after initial combined therapy.[31,53] We recommend combined-modality treatment because some recurrences are not resectable and others lead to metastasis.

Midline Granuloma

Smalley and coworkers[71] reported on 33 patients who received radiation therapy with curative intent at the Mayo Clinic between 1936 and 1983. Eleven patients (33%) developed local failure, the majority before 3 years. Local control was achieved in 4 (44%) of 9 patients who received 3000 to 4000 cGy, and in 15 (71%) of 21 patients who received higher doses ($P = .08$). Some component of marginal failure occurred in five patients. Three patients developed diffuse histiocytic lymphoma at 2, 3, and 18 years after treatment, respectively. Three patients developed lymph node failures, and six patients had systemic spread. The overall 10- and 20-year relapse-free rates were 60% and 40%, respectively. Women had higher survival rates than men ($P = .04$). The presence of B symptoms had no prognostic significance.

University of Florida Results With Radiation Therapy of Malignant Neoplasms

Between October 1964 and December 1983, 48 patients with malignant tumors of the nasal cavity (31 patients), ethmoid sinus (13), or sphenoid sinus (4) were treated with curative intent by radiation therapy at the University of Florida. There were 21 squamous cell carcinomas, 14 minor salivary gland tumors (7 adenocarcinomas, 6 adenoid cystic carcinomas, and 1 mucoepidermoid carcinoma), 3 malignant melanomas, 2 soft tissue sarcomas, and 8 esthesioneuroblastomas. Lymphomas, plasmacytomas, and primary tumors of bone were excluded from this analysis. Forty-two patients were treated with irradiation alone, and six with planned combined irradiation and surgery (two with preoperative irradiation, four with postoperative irradiation).

The probability of local control at 10 years for stage I (7 patients) was 100%; for stage II (19 patients), 53%; and for stage III (22 patients), 30% (Fig. 22-40). Of 24 failures at the primary site, 10 occurred more than 24 months after completion of irradiation. With the exception of adenoid cystic carcinoma (17% local control at 15 years), the ultimate local control rates for all histologic types were in the range of 40% to 60% (Fig. 22-41). Although adenoid cystic carcinomas were initially responsive, five of six patients with these tumors developed late primary recurrence at 40, 48, 60, 60, and 148 months, respectively. Salvage treatment was attempted in eight patients, but was successful in only two. Surgical salvage was not attempted in the remaining 16 patients, most often because of unresectable disease.

Of seven patients with documented intracranial extension, three patients (43%) remained free from local recurrence 3.5, 4, and 9 years after treatment, respectively.

Death due to neck failure alone was not observed. Forty-four patients presented with necks that were clinically negative for disease. Elective neck irradiation was given to 22 patients; none developed neck failure. Two of the 22 patients who were not given elective treatment developed recurrence in the neck in the absence of primary failure; both were salvaged by neck dissection. Four patients (two adenocarcinomas, one melanoma, one esthesioneuroblastoma) with apparent disease control above the clavicles died of distant metastases alone. The 5-, 10-, 15-, and 20-year uncorrected actuarial survival rates for all 48 patients were 52%, 30%, 22%, and 22%, respectively (Fig. 22-42). Continuous disease-free survival rates at 10 years, according to stage, were 86% for stage I, 42% for stage II, and 22% for stage III (Fig. 22-43). The single failure in a patient with stage I disease

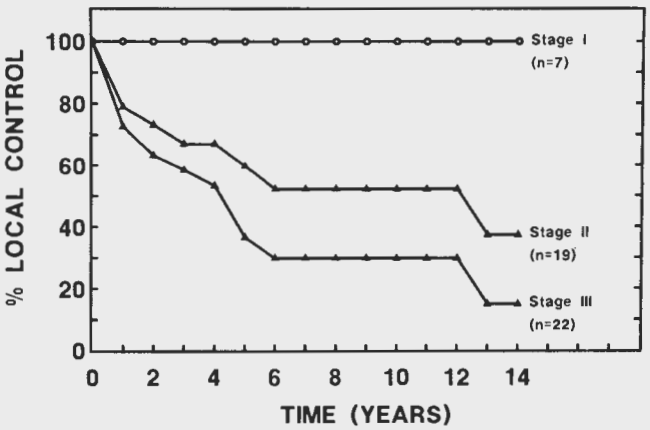

Figure 22-40. Actuarial local control according to tumor stage, for all histologic types combined. (Parsons JT, Mendenhall WM, Mancuso AA, Cassisi NJ, Million RR. Malignant tumors of the nasal cavity and ethmoid and sphenoid sinuses. Int J Radiat Oncol Biol Phys 1988;14:18)

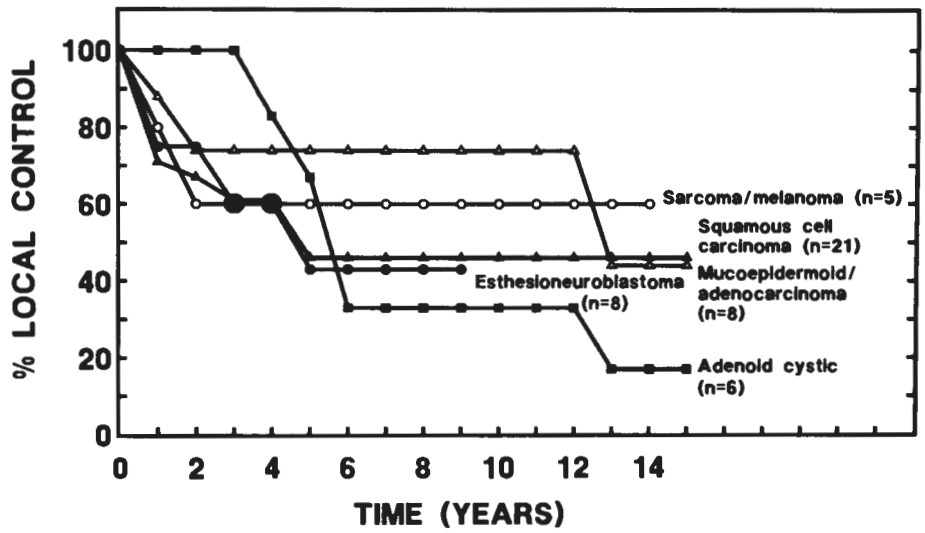

Figure 22-41. Actuarial local control according to histologic type, for all stages combined. (Parsons JT, Mendenhall WM, Mancuso AA, Cassisi NJ, Million RR. Malignant tumors of the nasal cavity and ethmoid, and sphenoidal sinuses. Int J Radiat Oncol Biol Phys 1988;14:18)

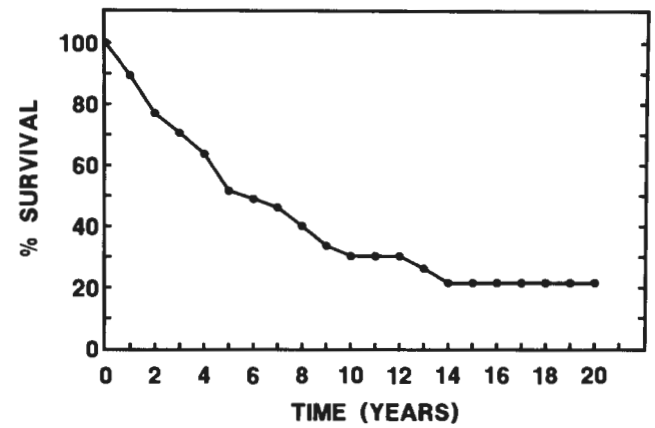

Figure 22-42. Actuarial survival for all 48 patients. (Parsons JT, Mendenhall WM, Mancuso AA, Cassisi NJ, Million RR. Malignant tumors of the nasal cavity and ethmoid and sphenoid sinuses. Int J Radiat Oncol Biol Phys 1988;14:19)

was a lymph node metastasis that was successfully managed by radical neck dissection.[56]

The 10-year continuous disease-free survival rate for 8 patients with mucoepidermoid carcinoma or adenocarcinoma was 47%; for 21 patients with squamous cell carcinoma, 42%; for 6 patients with adenoid cystic carcinoma, 33%; for 5 patients with sarcoma or malignant melanoma, 30%; and for esthesioneuroblastoma, 25%.

Maxillary Sinus

Squamous Cell Carcinoma

Jesse reviewed 63 patients with previously untreated squamous cell carcinoma of the maxillary antrum who received treatment with curative intent at the M. D. Anderson Hospital between 1952 and 1961.[30] Patients treated between 1952 and 1957 generally received postoperative irradiation (5000 cGy in 4 weeks) after radical

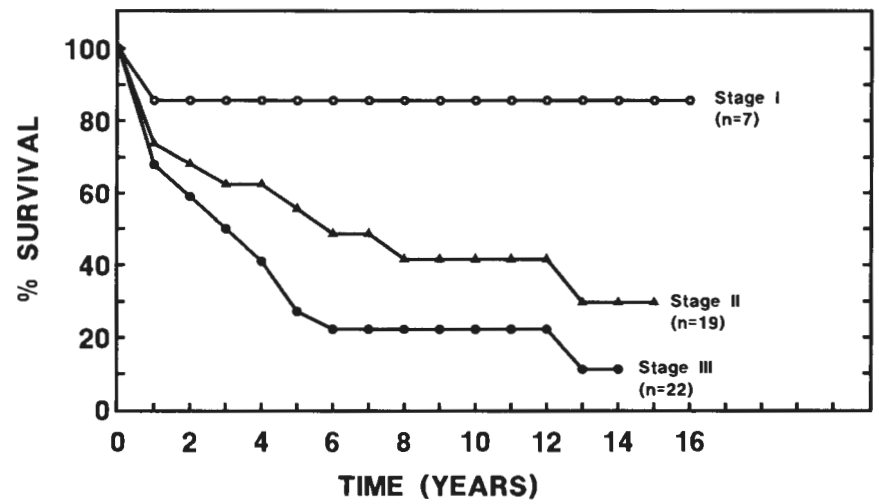

Figure 22-43. Continuously disease-free survival according to tumor stage. (Parsons JT, Mendenhall WM, Mancuso AA, Cassisi NJ, Million RR. Malignant tumors of the nasal cavity and ethmoid and sphenoid sinuses. Int J Radiat Oncol Biol Phys 1988;14:19)

maxillectomy; the 3-year survival rate was 39%. Between 1958 and 1961, preoperative irradiation (5000 to 6000 cGy in 5 to 6 weeks) produced a 3-year survival rate of 45%. Operative morbidity rate was higher in the preoperative irradiation group. The 3-year survival rate after surgery alone for selected lesions was 45% (9 of 20).

Kurohara and coworkers[34] reported on 174 patients with squamous cell carcinoma of the maxillary sinus and negative lymph nodes treated at the Roswell Park Memorial Institute (Buffalo, NY) between 1925 and 1963. Radiation therapy alone produced 5-year survival in 13 (35%) of 37 patients with T1–2 lesions and 10 (10%) of 100 patients with T3–4 disease. Radical surgery plus irradiation was used in only seven T1–2 patients. For T3–4 disease, resection followed by irradiation produced 5-year survival in 6 (29%) of 21 patients.

Lee and Ogura[38] reported on 96 patients with maxillary sinus carcinomas who received treatment at Washington University (St. Louis) from 1960 to 1976; 74 (77%) had squamous cell carcinoma. After preoperative irradiation (mostly 5000 to 7000 cGy) and surgery, 5-year absolute no-evidence-of-disease survival rates were 60%, 45%, 28%, and 38% in patients with T1, T2, T3, and T4 tumors, respectively. Radiation therapy alone (mostly 6000 to 7400 cGy) failed to produce a single 5-year survivor among 23 patients (2 with T2, 6 with T3, and 15 with T4 tumors).

St. Pierre and Baker[75] reported on 66 patients with squamous cell carcinoma of the maxillary sinus treated at the University of Michigan (Ann Arbor) between 1964 and 1975. Eighty-seven percent of patients had T3 or T4 disease. Five-year survival rates were 16% after radiation therapy alone, 20% after surgery alone, and 58% after combined treatment. Five-year survival rates were 75%, 29%, and 20% for T2, T3, and T4 lesions, respectively. No patient developed distant or regional lymph node failure who did not also have recurrence at the primary site.

Isaacs and coworkers[29] reviewed a small series of patients with squamous cell carcinoma treated at the University of Florida between 1966 and 1984. Thirty-two patients had T3 or T4 disease. Three of nine patients treated by combined surgery and radiotherapy were alive at 2 years. Six (26%) of 23 patients treated with radiotherapy alone were alive at 2 years, but only one survived 5 years.

Amendola and associates[4] reported a 35% 5-year survival rate and a 35% rate of continuous disease control at the primary site (3 years minimum follow-up) in 20 patients (2 with T2, 18 with T4 tumors) with squamous cell carcinoma of the maxillary antrum treated by radiation therapy alone. Bataini and Ennuyer reported the Curie Foundation results for 27 patients with squamous carcinoma of the maxillary antrum treated by supervoltage radiation therapy between 1959 and 1965.[9,23] Only three patients had limited primary disease. The 3- and 5-year disease-free survival rates were 11 (41%) of 27 patients and 6 (32%) of 19 patients, respectively.

Frich irradiated 18 patients with T3–4 squamous cell carcinoma of the maxillary sinus with curative intent. Six patients (33%) remained continuously free of disease for over 5 years after doses of 6000 to 7000 cGy. Local control was obtained in six of eight suprastructure and zero of seven infrastructure lesions.[9,23]

In summary of the above studies, it is reasonable to expect 5-year survival rates of about 60% to 70% for T1 and T2 lesions, and 30% to 40% for T3 and T4 lesions after resection and postoperative irradiation. Poor prognostic factors include positive lymph nodes, erosion of the pterygoid plates, pterygopalatine fossa invasion, and orbital invasion.[26,72] For advanced, unresectable disease, average 5-year survival rates of 10% to 15% are achieved with high-dose irradiation alone.

Adenoid Cystic Carcinoma

Goepfert and associates reported on 33 patients with adenoid cystic carcinoma who received treatment with curative intent at the M. D. Anderson Hospital between 1951 and 1980.[24] Eight (24%) of 33 patients remained free of disease for 5 or more years after treatment, which most commonly consisted of surgery and postoperative irradiation (23 patients). Patients were divided into high- and low-grade histologic groups, depending on whether solid areas made up more or less than 30% of the tumor. Eight (47%) of 17 patients with low-grade lesions remained free of disease beyond 5 years, whereas there were no 5-year disease-free survivors in 16 patients with high-grade tumors. Distant metastases (five bone and six lung) were noted in two patients with low-grade disease and in nine patients with high-grade tumors.

The finding of poorer prognosis in patients with a solid histologic pattern has been confirmed by others.[45,59]

Rafla[60] reported on 16 of Lederman's patients from the Royal Marsden Hospital (London) with adenoid cystic carcinoma of the nasal cavity and paranasal sinuses. In 10 of the 16 patients, the tumor arose in the maxillary antrum. Half of the patients received radiation therapy alone, and half received surgery plus radiation therapy. Three (23%) of 13 patients who were at risk for 5 years remained alive and disease free at that time.

Leafstedt and coworkers[36] reported the Roswell Park Memorial Institute results for nine patients with adenoid cystic carcinoma of the maxillary sinus who were treated between 1940 and 1965. Most patients received surgery alone. No cures were achieved.

FOLLOW-UP POLICY

Nasal Vestibule

Frequent follow-up for 3 years is important because recurrences often are salvaged by second-line treatment. Particular attention is paid to the regional lymphatics.

Nasal Cavity and Paranasal Sinuses

If a maxillectomy has been done, follow-up is simplified by the ease of physical examination; it is much more difficult to assess disease status after radiation therapy alone, and Caldwell-Luc or ethmoid sinus exploration may be necessary for suspicious symptoms. Baseline CT or MRI is obtained about 3 months after treatment and is repeated every 6 months for 3 years thereafter.

In general, CT is preferred for follow-up of paranasal sinus cancer, since the earliest sign of recurrence may be a new focus of bone invasion. Inverted papillomas, in particular, should be followed with CT. Nasal cavity lesions may be followed by MRI or CT. The relative values of CT and MRI in the diagnosis of sinonasal neoplasms are discussed in detail earlier in this chapter and in Chapter 4.

COMPLICATIONS OF TREATMENT

Maxillary Sinus

Complications of radiation therapy for maxillary sinus cancer include osteonecrosis, radiation-induced central nervous system disease, loss of vision, nasal obstruction, and otitis media. Complications of maxillectomy include nasal crusting, nasal speech, the requirement for a prosthesis, diplopia and loss of visual acuity (when the eye is saved), trismus, hemorrhage, and bad odor.

Ethmoid Sinus and Nasal Cavity

Surgery

Complications of ethmoid sinus surgery include total blindness, loss of ocular motility, hemorrhage, anesthesia complications, meningitis, cerebrospinal fluid leak, cellulitis and pansinusitis, brain abscess, stroke, fistula between the cavernous sinus and internal carotid, and damage to the frontal lobe.[43,44] Potential complications of the craniofacial procedure were reported by Ketcham and coworkers.[32] About one third of patients had a life-threatening complication requiring intensive care and prolonged hospitalization. The operative mortality rate was 4%. Complications included meningitis, pneumocephalus, subdural abscess, cerebrospinal fluid leak, diplopia, and hemorrhage. Most of these patients had recurrent or far-advanced disease before surgery. In more recent series, the risk of severe complications has decreased to 10% to 20%; the operative mortality rate remains at 3% to 5%.[16,65,76] Sundaresan and Shah[76] reported epidural infection in 6 of 30 patients who underwent craniofacial resection of anterior skull base tumors; the bifrontal bone flap had to be removed in all 6 patients.

Irradiation

In the University of Florida series,[56] 5 (10%) of 48 patients developed transient central nervous system syndrome, consisting of vertigo, headaches, decreased cerebration, and lethargy. One patient developed a cerebrospinal fluid leak, ataxia, and disorientation during a course of radiation therapy after 5500 cGy had been administered. Symptoms abated after a 1-week rest. There was no documented brain necrosis or radiation myelitis.

No soft tissue necroses occurred. Three patients developed bone exposures of the maxilla; two were precipitated by dental extractions. Complications were minimally symptomatic and resolved spontaneously in two of three patients. In the third, extensive surgical débridement was required, resulting in a permanent oral–antral fistula.

Small (less than 1 cm), asymptomatic nasal septal perforations were incidentally noted in two patients at 5 and 7 months, respectively. One patient developed nasal synechiae leading to unilateral occlusion, and two others developed about 50% stenosis. This problem usually can be avoided by using petrolatum swabs and nasal douches with a dilute saline solution until mucosal healing is complete.

EYE. Unilateral blindness secondary to radiation retinopathy or optic nerve injury occurred in 16 (33%) of 48 patients between 6 and 60 months after treatment (mean, 25 months; median, 26 months). Four patients (8%) (two with stage II malignant melanoma of the nasal cavity, one with stage II squamous cell carcinoma of the nasal cavity, and one with stage III recurrent esthesioneuroblastoma) developed bilateral blindness due to bilateral optic neuropathy (two patients) or a combination of ipsilateral radiation retinopathy and contralateral optic neuropathy (two patients). In none of the four patients who developed bilateral blindness was either orbit definitely involved by tumor. Onset of blindness in the second eye occurred at 17, 35, 46, and 90 months, respectively. Since not all patients survived long enough to be at risk for development of blindness secondary to treatment, an actuarial cumulative probability of developing unilateral or bilateral blindness was calculated, scoring death without visual loss as a censoring event (Fig. 22-44). Sixty-three percent of patients who survived for 8 to 15 years after radiation therapy developed unilateral blindness, and 15% were bilaterally blind.

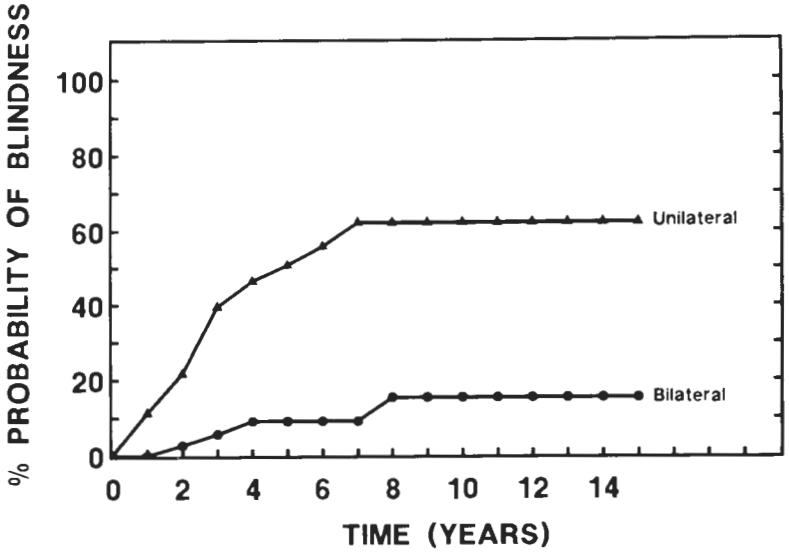

Figure 22-44. Actuarial probability of developing unilateral or bilateral blindness after irradiation. (Parsons JT, Mendenhall WM, Mancuso AA, Cassisi NJ, Million RR. Malignant tumors of the nasal cavity and ethmoid and sphenoid sinuses. Int J Radiat Oncol Biol Phys 1988;14:20)

Efforts to alleviate the problem of bilateral blindness should focus on reducing the dose to the optic nerves and improving the homogeneity of dose within the treatment volume. Although CT and MRI offer considerable help in planning tighter treatment volumes around the eye, they are not of much help with regard to the optic nerves, which are situated so that portions of both usually remain in the treatment volume for the entire treatment.

A change in philosophy in the management of these lesions has occurred in the last several years at the University of Florida. Lesions that are resectable are first treated surgically, and then the dose of irradiation is limited to approximately 6000 cGy at 180 cGy per fraction once a day, or 6000 cGy at 110 cGy per fraction twice a day (6 hours minimum between fractions). Unfortunately, many tumors are unresectable, or patients are medically inoperable or refuse an operation of such magnitude. Off-axis dosimetry at the level of the optic nerves and known time–dose relationships are important factors in treatment planning. A customized tissue compensator for the anterior portal may improve the dose homogeneity. Hyperfractionation may result in differential sparing of the optic nerve relative to acute-effects normal tissues and tumor. High-energy electrons generally are not used around the eyes, except in unusual circumstances.

Nasal Vestibule

Irradiation of nasal vestibule carcinoma may result in nasal synechiae and occlusion of the nasal passages. Stenosis usually is preventable by mechanically dilating the nose with cotton-tipped applicators coated with petrolatum twice daily until mucosal healing is complete. Irradiation also produces dryness of the mucous membranes. Crusting is eliminated by douching the nose with a dilute saline solution once or twice daily. Severe necroses of cartilage, soft tissue, and bone of the maxilla are uncommon. Small, asymptomatic defects in the nasal septum that have been caused by tumor growth often persist after irradiation, but do not require surgical repair. Small pits in the nasal dorsum at the locations of the implanted radium needles may persist after high-dose interstitial treatments.

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23

NASOPHARYNX

WILLIAM M. MENDENHALL, RODNEY R. MILLION, ANTHONY A. MANCUSO, AND SCOTT P. STRINGER

Malignant tumors of the nasopharynx are uncommon in the United States, accounting for only a small percentage of all malignancies of the head and neck. The age-adjusted mortality rates for American whites and blacks have not changed appreciably from 1950 to 1979.[28] The highest mortality rate for white males in the United States is along the Gulf and Atlantic coasts; this pattern is less apparent for white females.[28]

The high incidence reported in China is centered on the southeastern coast among the Cantonese population of Kwangtung Province, including Hong Kong and Macao. The age-standardized incidence of nasopharyngeal carcinoma in males in parts of the Kwangtung Province of China is nearly 150 per 100,000 compared with less than 1 in 100,000 in the United States.[48] The remainder of China has an intermediate to normal incidence. United States' statistics show that immigrant Chinese have a greater risk of developing a malignancy of the nasopharynx than those born in the United States, and the excess risk is maintained to a certain extent in subsequent generations. The risk of nasopharyngeal cancer in Chinese–American males is six times higher than that of any other ethnic group.[28] The risk is not associated with Asians in general, since the rate is low in Japanese.

A number of possible factors have been suggested, such as inhalation of incense smoke containing nitrosamines, genetic susceptibility, and the Epstein-Barr virus (EBV).[3,25,27] The EBV is primarily associated with World Health Organization (WHO) type 2 and 3 nasopharyngeal carcinoma[13,34]; a higher proportion of nasopharyngeal cancers appear to be EBV associated in endemic areas such as southern China.[25] The immunoglobulin A (IgA) antibody to Epstein-Barr viral capsid antigen (VCA) and early antigen have been found to be significantly associated with nasopharyngeal cancer, and the relative risk increases with increasing antibody titers, so that these may be used in mass screening programs in endemic areas.[25,27,47,49] Ho and others[3,22,48] have suggested that the high incidence of carcinoma of the nasopharynx in the boat people of Hong Kong may be related to a diet of salted fish fed to young children. The salted fish contains nitrites, which are converted to volatile nitrosamines in the absence of vitamin C. Nitrosamines are known to produce nasal carcinomas in Wistar albino rats and Syrian golden hamsters.[48] Dermatomyositis, a paraneoplastic syndrome associated with various malignancies, has been reported to be associated with just under 1% of patients with nasopharyngeal cancer.[43]

A 3 : 1 predominance of the disease occurs in males.[29] The age distribution is much younger than for cancer of other sites of the head and neck.[29] Fifteen percent to 20% of patients are younger than 30 years of age; a 5-year-old patient with carcinoma has been reported.

ANATOMY

Gross Anatomy

The anatomic features and relationships of the nasopharynx in a midsagittal section are shown in Figure 23-1.[16] The nasopharynx is roughly cuboidal with two lateral walls and a sloping roof, which is continuous with the posterior wall. The pharyngeal surface of the soft palate forms a mobile floor of the nasopharynx. The nasopharynx is in direct continuity with the nasal cavity, the oropharynx, and the middle ears by way of the eustachian tubes. The transverse diameter is about 3 cm anteriorly and 4 to 5 cm posteriorly at the level of Rosenmüller's fossa. The nasopharynx has an anteroposterior diameter of 2 to 4 cm. The distance from the skin of the upper lip to the posterior wall of the nasopharynx, as measured through the nasal cavity, is usually 7 to 8 cm in adults. The mucosa of the roof and posterior wall is often irregular owing to the presence of the pharyngeal bursa, tonsil (adenoids), and hypophysis. A variety of views of the normal nasopharynx is given in Figure 23-2. The mucosa

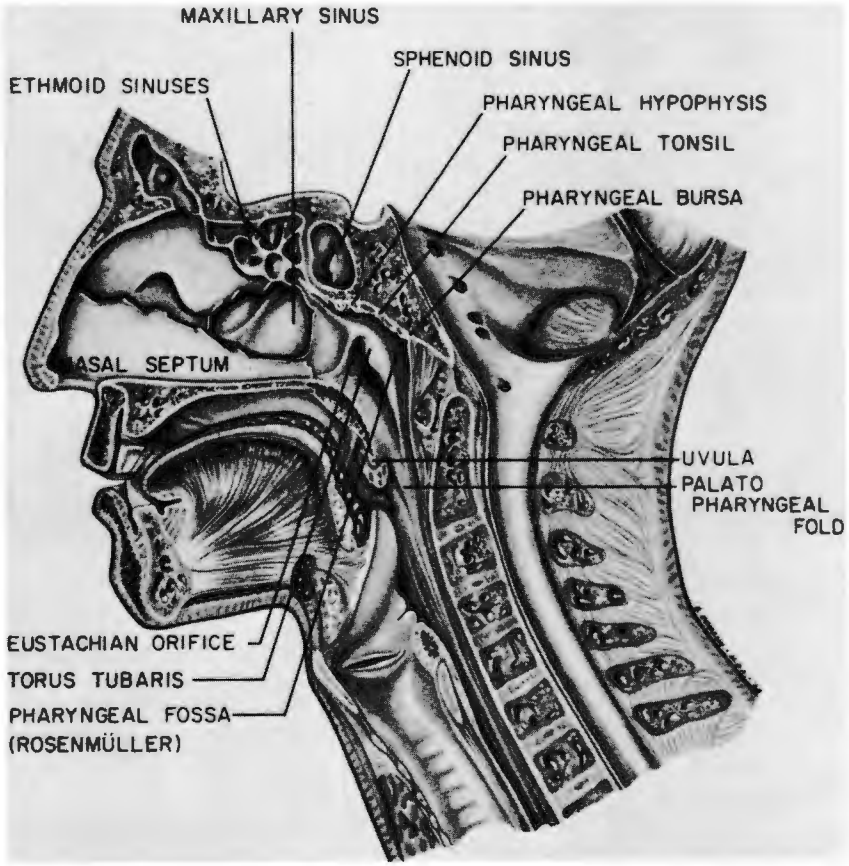

Figure 23-1. Midsaggital section of the head, showing the nasopharynx and related structures. (Fletcher GH, Healey JE Jr, McGraw JP, Million RR. Nasopharynx. In: MacComb WS, Fletcher GH, eds. Cancer of the head and neck, Baltimore, Williams & Wilkins, 154. Copyright © 1967)

tends to become smooth and atrophied with age, but many folds may remain in the later years of life, and add to the examiner's confusion as to whether a tumor is present. Submucosal lymphoid tissue may persist well past puberty and may even be present in elderly people. After successful radiation therapy, the mucosa changes to a smooth, atrophic appearance.

The lateral walls include the eustachian tube openings, marked by the prominent and rounded posterior lips (torus tubarius) created by the underlying cartilaginous portion of the tube (Fig. 23-3). In the resting state, the torus appears prominent and rounded, but if the patient is gagging or swallowing, constriction of the muscles causes elongation and flattening of the appearance of the lateral wall. The so-called tubal tonsil, as such, does not exist.[8] Lymphoid tissue is present nearby in the submucosa of the fossa of Rosenmüller. Just behind the adenoids on the posterior wall is an inconstant blind sac or depression, the pharyngeal bursa, but this is not often identified. Anterior to the adenoids is the pharyngeal hypophysis landmark, which is also not easily identified. The pharyngeal hypophysis may consist of remnants of hypophyseal tissue derived from the craniopharyngeal canal (Rathke's pouch) and may be the rare site of origin of a craniopharyngioma.

Deep to the mucous membrane is the well-defined pharyngeal aponeurosis, which attaches to the bones of the base of skull and cervical spine. The line of attachment is outlined in Figure 23-4. Deep to the aponeurosis is the muscular wall, made up primarily of the superior constrictor muscle. The muscular wall is incomplete near the base of the skull, leaving a small muscular defect, the sinus of Morgagni (Fig. 23-5), through which the eustachian tube enters the nasopharynx. Therefore, tumor has only to penetrate the mucosa and the aponeurosis in this area to gain access to the parapharyngeal space and the central base of the skull.

The foramen lacerum is directly related to the roof of the nasopharynx (Fig. 23-6). The lower part of the foramen lacerum is filled with fibrocartilage. The internal carotid artery runs just above the foramen lacerum as it enters the cavernous sinus. A whole-organ sagittal section demonstrating the relationship of the nasopharynx to the sphenoid and posterior ethmoid sinuses is shown in Figure 23-7.

The blood supply to the nasopharynx is mainly through the ascending pharyngeal branch of the external carotid artery, the artery of the pterygoid canal (the vidian artery), and the sphenopalatine artery. Venous drainage is to a plexus of pharyngeal veins on the outer surface of the muscular wall. This plexus then drains to the pterygoid plexus and the internal jugular vein. Alternatively, the pharyngeal plexus may communicate with the orbital cavity by way of the inferior orbital vein.

The sensory nerves are the glossopharyngeal and the maxillary division of the trigeminal nerve, the latter supplying the anterior portion of the nasopharynx. Motor supply is from the vagus nerve, except for the tensoris veli palatini (trigeminal) and stylopharyngeus (glossopharyngeal).

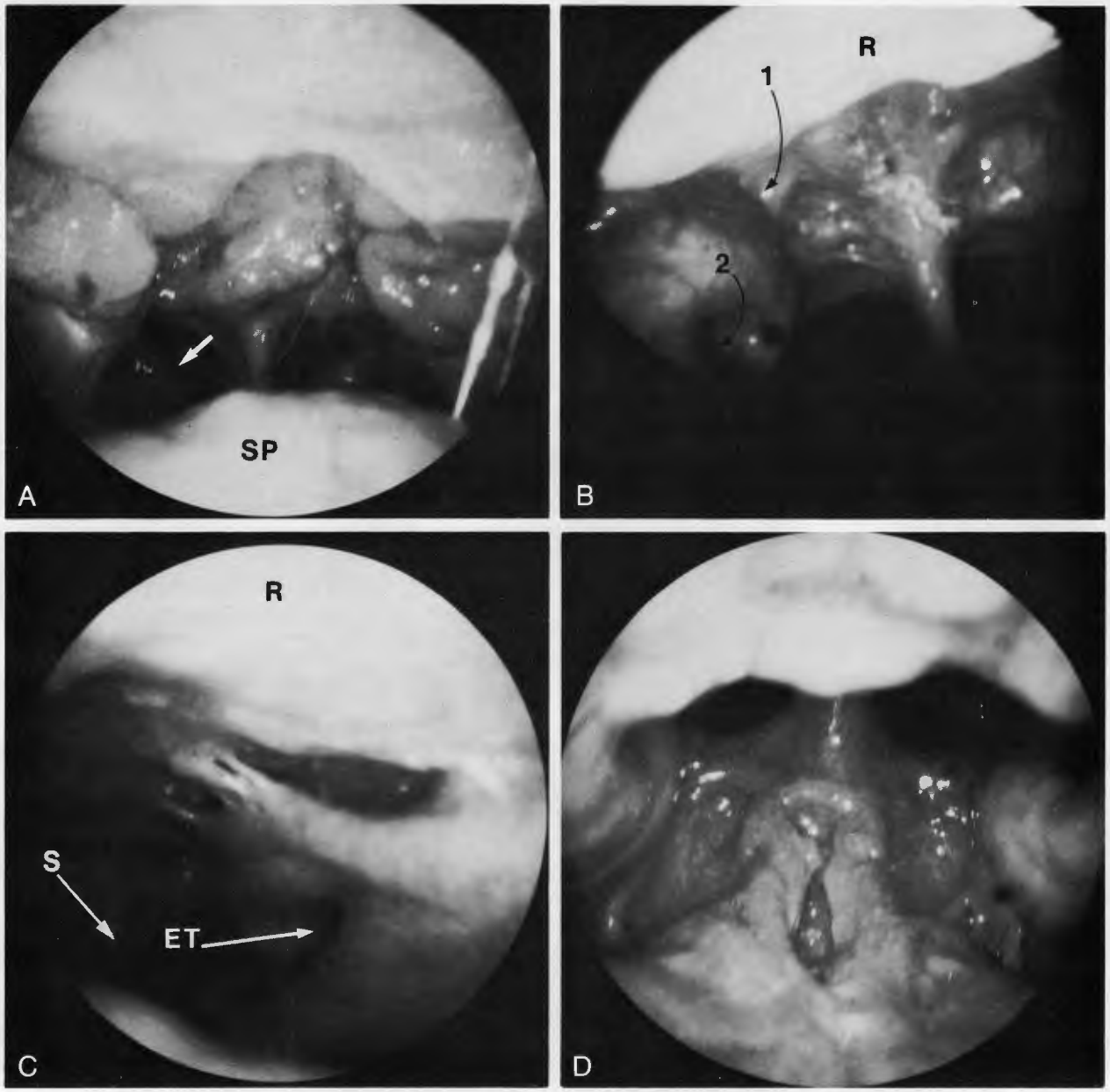

Figure 23-2. Nasopharynx as viewed with the Storz laryngoscope. Photographs are oriented with the soft palate below and the roof to the top of the image (see Chap. 3). (*A*) Normal nasopharynx in a 76-year-old man. Note prominent lymphoid tissue in anterior roof, filling both fossae of Rosenmüller. Arrow points to inferior nasal turbinate. (*SP*, soft palate). (*B*) Normal nasopharynx in an 80-year-old man. Arrow 1 points to left fossa of Rosenmüller. Arrow 2 points to eustachian tube opening. R, roof of nasopharynx. (*C*) Synechiae between torus tubarius and roof of nasopharynx. R, roof; ET, entrance to eustachian tube; S, nasal septum. (*D*) Normal nasopharynx in a 50-year-old man.

Lymphatics

An extensive submucosal capillary lymphatic plexus exists, explaining the high incidence of neck metastases. The tumor spreads initially to the retropharyngeal, junctional, and jugulodigastric lymph nodes, and then along the internal jugular and spinal accessory chain.

Although the majority of lymphatic channels empty into either the retropharyngeal, junctional, or jugulodigastric lymph nodes, inconstant lymphatic vessels are described as passing directly to the nodes below the bifurcation of the carotid (midjugular nodes) and to the spinal accessory nodes.[40]

The retropharyngeal nodes are an important route of spread. The lateral retropharyngeal nodes (nodes of Rouvière) lie in the retropharyngeal space near the lateral border of the posterior pharyngeal wall and medial to the carotid artery (Fig. 23-8). Directly behind the

(text continues on page 604)

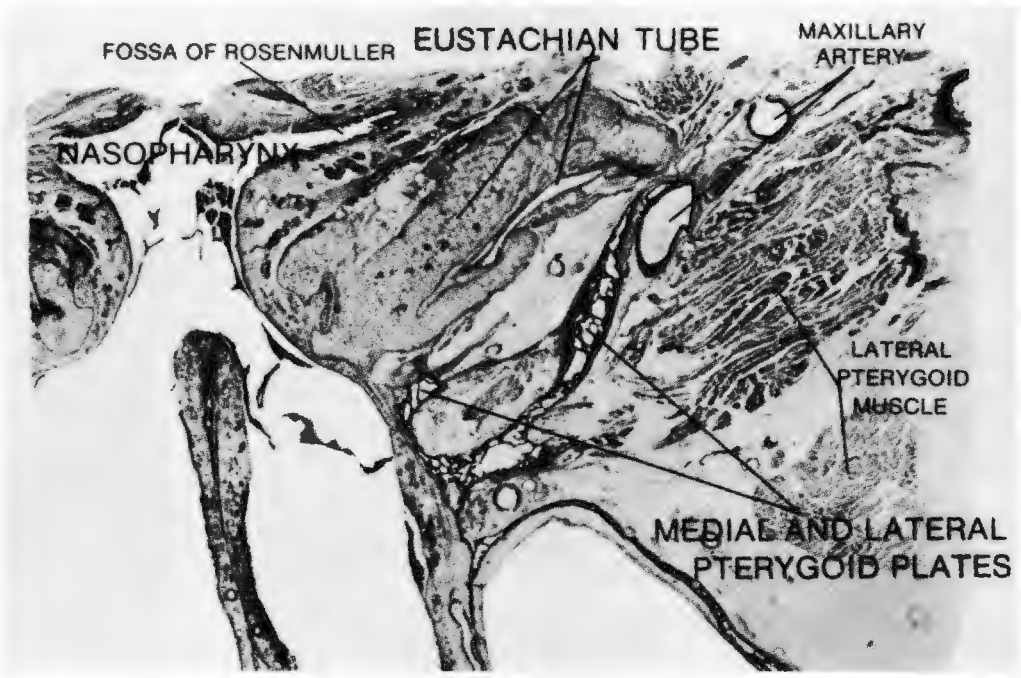

Figure 23-3. Horizontal section through the nasopharynx. Fossa of Rosenmüller created by protrusion of tube cartilage into lateral wall. (Bridger MWM, van Nostrand AWP. The nose and paranasal sinuses: applied surgical anatomy. J Otolaryngol 1978;7:24)

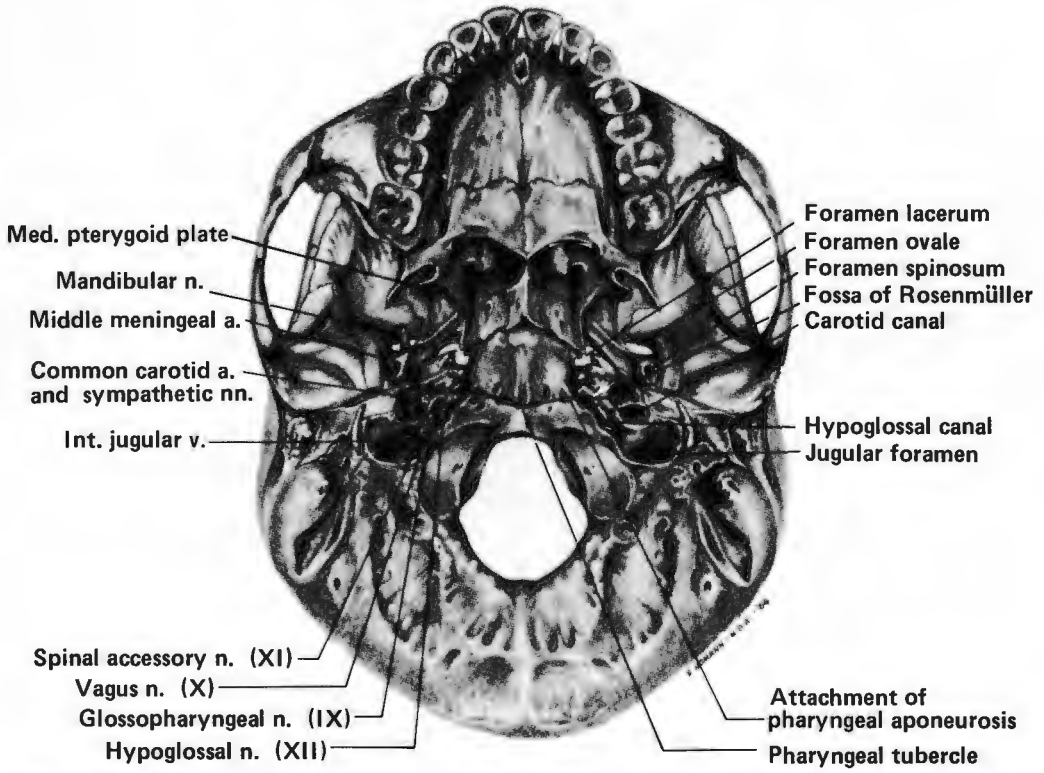

Figure 23-4. Basal view of skull to show the bony attachments of the nasopharyngeal wall. The bony formation of the base of the skull are shown on the right, and structures occupying these foramina on the left. (Fletcher GH, Healey JE Jr, McGraw JP, Million RR. Nasopharynx. In: MacComb WS, Fletcher GH, eds. Cancer of the head and neck. Baltimore, Williams & Wilkins, 155. Copyright © 1967)

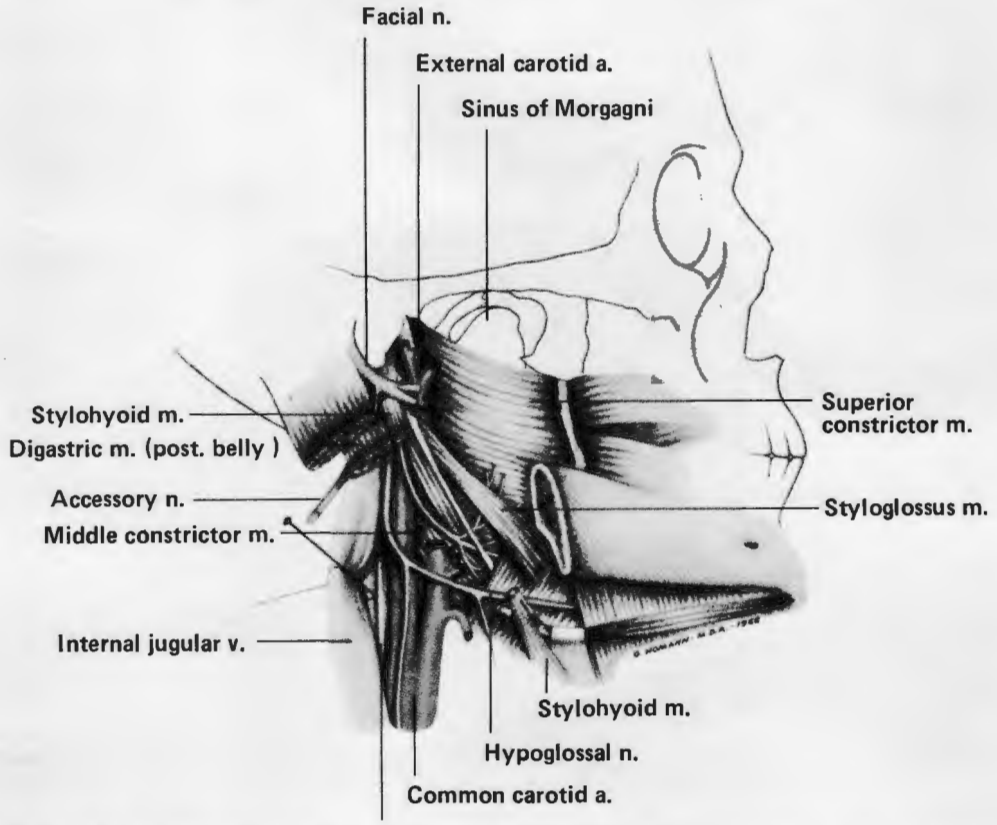

Figure 23-5. Lateral wall of nasopharynx with related structures. (Fletcher GH, Healey JE Jr, McGraw JP, Million RR. Nasopharynx. In: MacComb WS, Fletcher GH, eds. Cancer of the head and neck. Baltimore, Williams & Wilkins, 161. Copyright © 1967)

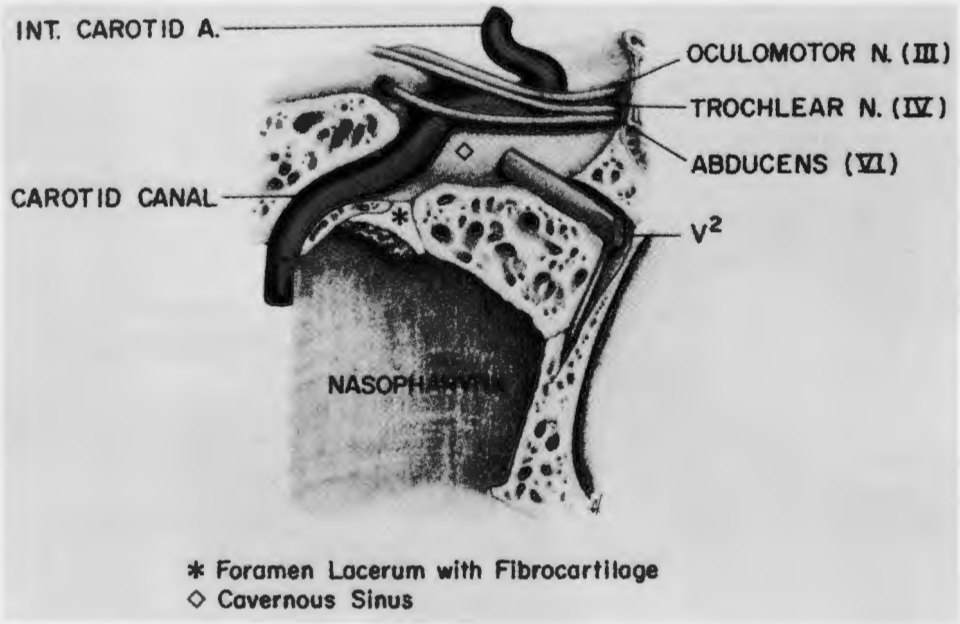

Figure 23-6. Sagittal section through cavernous sinus, foramen lacerum, and nasopharynx, showing the interrelationships of these three structures. (Fletcher GH, Healey JE Jr, McGraw JP, Million RR. Nasopharynx. In: MacComb WS, Fletcher GH, eds. Cancer of the head and neck. Baltimore, Williams & Wilkins, 156. Copyright © 1967)

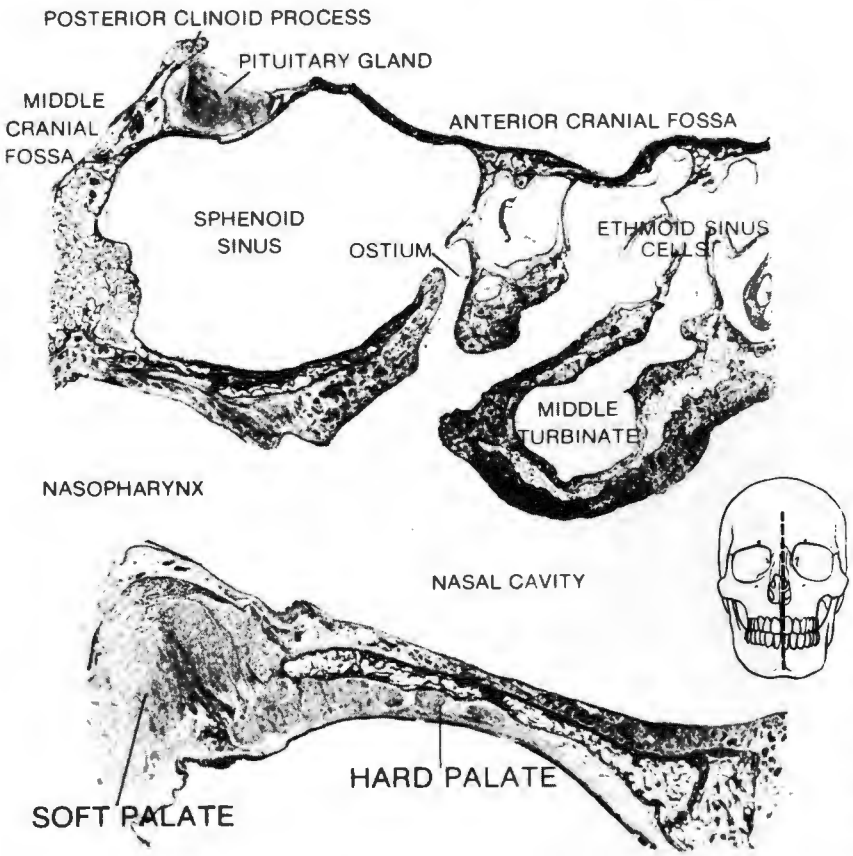

Figure 23-7. Sagittal section through nasopharynx and sphenoid sinus, just to the left of midline. Note relationship of sphenoid sinus ostium to nasopharynx and posterior nasal cavity. The anterior wall of the sphenoid sinus and the floor of the pituitary are thin bone. (Bridger MWM, van Nostrand AWP. The nose and paranasal sinuses: applied surgical anatomy. J Otolaryngol 1978;7[Suppl 6]:21)

nodes are the lateral masses of the atlas (C1). According to Rouvière,[40] usually one node occurs on each side, but occasionally two, and rarely three, nodes are found, and they may be found as low as the hyoid (C3) level. These nodes are said to atrophy with age and may be absent on one side, but are rarely absent entirely.

Rarely do patients have a clinically involved lymph node of the parotid area. This route of spread is possible from the lymphatics of the eustachian tube, which may drain by way of the lymph vessels of the tympanic membrane and external auditory canal to the parotid area lymph nodes.[40]

PATHOLOGY

Carcinomas comprise about 85%, and lymphomas about 10%, of the malignant lesions of the nasopharynx. The WHO has classified nasopharyngeal carcinomas as follows[5]:

WHO-1: Squamous cell carcinoma
WHO-2: Nonkeratinizing carcinoma
WHO-3: Undifferentiated carcinoma

Lymphoepithelioma is included in the WHO-3 category.[5,34] Approximately 25% of nasopharyngeal carci-

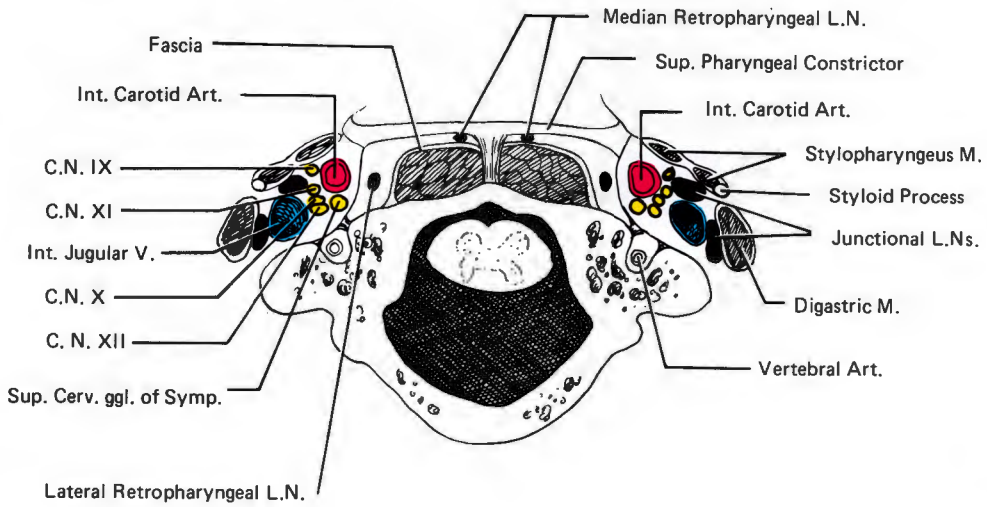

Figure 23-8. Retropharyngeal lymph nodes.

nomas in white North Americans are WHO-1 type.[34] A miscellaneous group of malignant tumors of the nasopharynx or adjacent tissues includes melanoma, plasmacytoma, adenocarcinoma, sarcoma, chemodectoma, and unclassified malignancies. Benign lesions arising in or adjacent to the nasopharynx include juvenile angiofibroma and craniopharyngioma.

PATTERNS OF SPREAD

Primary

Nasopharyngeal carcinomas usually arise from the lateral posterior and superior wall of the nasopharynx. The nasopharyngeal surface of the soft palate is rarely the site of origin of a cancer, and is invaded secondarily in only advanced cases.

Many nasopharyngeal carcinomas, particularly WHO types 2 and 3, arise in the fossa of Rosenmüller.[35] The recognized spread to contiguous structures on admission, before treatment, in 99 patients with epithelial lesions is shown in Table 23-1.[17]

Inferior Extension

Inferior extension along the lateral pharyngeal walls and tonsillar pillars is recognized in almost one third of patients. Apparent posteroinferior spread of the tumor often is due to involvement of retropharyngeal nodes, although it occasionally may be due to extension of the primary tumor within the retropharyngeal space. Infiltration down the posterior pharyngeal wall usually is submucosal, and may result in invasion of the prevertebral muscles and eventually the clivus, or rarely the first cervical vertebra.

TABLE 23-1. Malignant Tumors of the Nasopharynx: Incidence of Spread to Contiguous Structures on Admission

Site of Spreod	No. Cases*
Oropharyngeal wall	29
Base of skull	25†
Tonsillar bed	15
Cranial nerves	12
Pterygoid fossa	9
Nasal cavity	5
Maxillary antrum	4
Orbit	3
Soft palate	3
Hard palate	2
Ethmoid sinuses	2
Hypopharynx	1

* In several patients, more than one structure was involved.

† Includes sphenoid sinus in 11 patients.

Note: M. D. Anderson Hospital data; patients treated August 1948 to December 1960.

(Fletcher GH, Million RR. Malignant tumors of the nasopharynx. Am J Roentgenol Radium Ther Nucl Med 1965;93:47. Copyright © 1965, Williams & Wilkins, Baltimore)

Anterior Extension

Extension into the posterior nasal cavity is common. Thorough shrinking of the nasal mucosa and examination with a small-diameter fiberoptic nasoscope is the best clinical method for detecting nasal cavity extension (Fig. 23-9). Invasion of the posterior ethmoids, the maxillary antrum, and the orbit occurs infrequently.

Superior Extension

Invasion into or through the base of the skull, including the sphenoid sinus, is recognized radiographically in at least 25% of patients before treatment.[10,17,34] Early, unrecognized invasion probably occurs in a far greater number of patients, since the base of the skull, brain, and cranial nerves are frequent sites of local recurrence. The favored site of early skull base invasion is the region of the foramen lacerum and petroclinoid fissure; the roof of the nasopharynx and the fossa of Rosenmüller lie immediately subjacent to this portion of the central skull base. Moreover, the tensor and levator veli palatini and pharyngobasilar fascia attach to this region of the skull base, and the parapharyngeal space is immediately subjacent. Both the muscular and fascial attachments and parapharyngeal space are ready conduits for spread of tumor to this portion of the skull base. Tumor also may eventually erode through the foramen ovale and destroy large portions of the floor of the middle cranial fossa and the petrous portion of the temporal bone. By these routes, the tumor eventually reaches the cavernous sinus, and thereby has access to the oculomotor, trochlear, trigeminal, and abducens nerves. The ophthalmic division and part of the maxillary division of the trigeminal nerve lie within the dural wall of the cavernous sinus, and are sometimes involved. Optic nerve and orbital invasion by tumor only occurs in advanced cases; there is usually associated destruction of the bone around the orbital apex. Orbital spread without bone invasion may occur via the inferior orbital fissure. The relationship of the nasopharynx to the sphenoid sinus, cavernous venous sinus, and cranial nerves is shown in Figure 23-10.

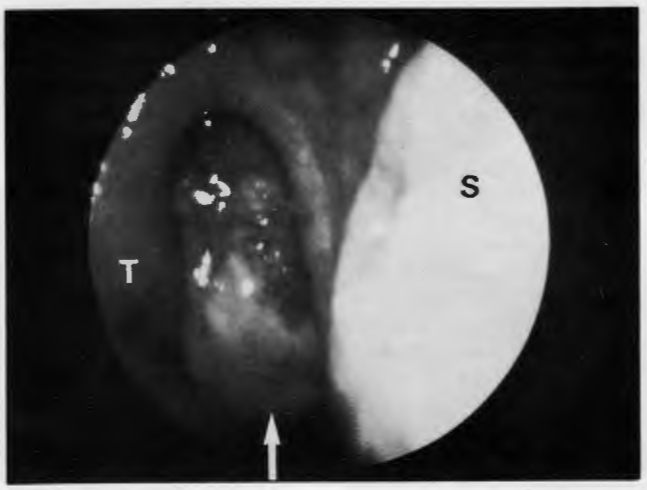

Figure 23-9. Carcinoma of the nasopharynx protruding about 1 cm into the right posterior naris. Photograph taken through fiberoptic nasoscope. Arrow points to tumor. S, septum; T, turbinate.

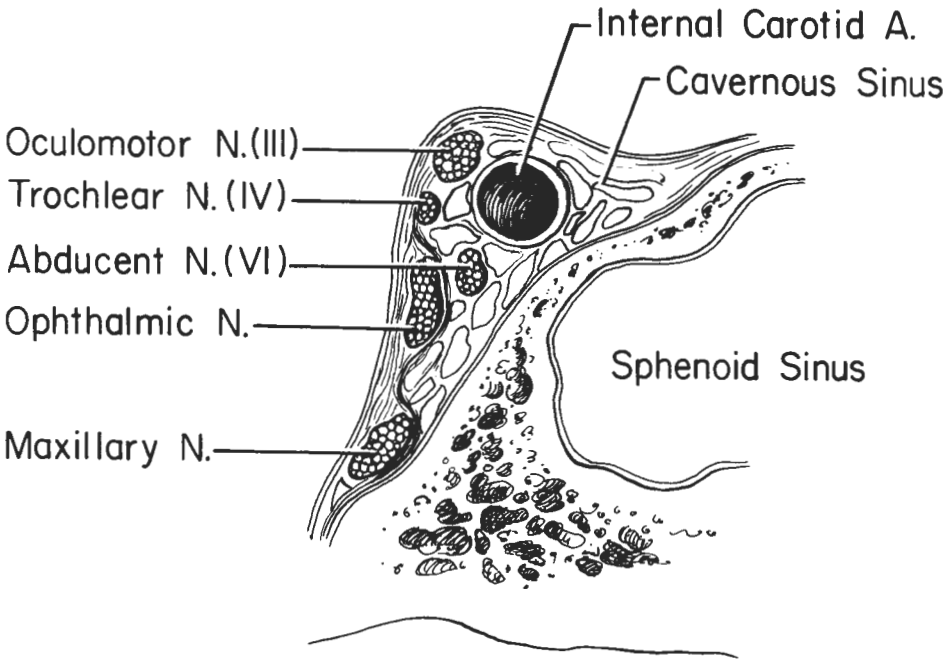

Figure 23-10. Coronal section of the cavernous sinus.

Tumor may invade the sphenoid sinus through its ostium or by direct penetration of the basisphenoid.

Lateral Spread

The lateral wall of the nasopharynx is incomplete superiorly. This defect, referred to as the sinus of Morgagni, is traversed by the cartilaginous portion of the eustachian tube and the levator veli palatini muscle, and provides an avenue of egress for the nasopharyngeal cancer to the parapharyngeal space and base of the skull. Cephalad spread to the skull base via the prestyloid parapharyngeal space was discussed in the previous section. Continued direct spread laterally and anteriorly from the prestyloid parapharyngeal space to the infratemporal fossa usually occurs in advanced tumors with destruction of the pterygoid plates.

Occasionally, far lateral spread can occur without bone destruction, or out of proportion to the amount of bone destruction present. Tumors that have spread laterally to involve the pterygoid plates will often invade the pterygopalatine fossa. The small fat pad present in the pterygopalatine fossa usually is symmetric. Obliteration of the fat pad here may herald subtle spread to the cavernous sinus along the second division of the trigeminal nerve or continued spread to the orbital apex, inferior orbital fissure, and perhaps, nasal cavity. The structures related to the lateral wall of the nasopharynx are shown in Figures 23-3 through 23-5, and in Figure 23-8.

Lateral spread of nasopharyngeal cancer may also extend to the poststyloid parapharyngeal space. This may be due to direct extension of tumor or spread to the lateral retropharyngeal lymph node. The carotid artery usually is not significantly affected by disease in this compartment, although compression with occlusion may occur in very advanced tumors. Tumor can follow the carotid artery into its foramen and canal and eventually the cavernous sinus, destroying adjacent bone along the way. The cervical sympathetic nerves and cranial nerves IX through XII are vulnerable to dysfunction caused by either direct lateral extension of tumor or compression by enlarged lymph nodes; the spinal accessory nerve is least often affected because of its more posterolateral position. In the past, a significant number of patients have recovered cranial nerve function after radiation therapy. This is probably because the nerves are compressed by enlarged retropharyngeal lymph nodes, rather than directly infiltrated by the primary tumor. Continued lateral spread of tumor along the inferior petrous apex and mastoid portion of the temporal bone rarely causes facial nerve dysfunction by spread to the fat pad just below the stylomastoid foramen, or to the middle ear and mastoid itself.

Lymphatics

Nasopharyngeal carcinoma usually spreads first to the retropharyngeal nodes and then to the junctional lymph nodes located beneath the mastoid tip, the posterior belly of the digastric muscle, and the sternocleidomastoid muscle[35] (see Fig. 23-8). The diffuse distribution of clinically positive nodes on admission is shown in Figure 23-11. Almost all patients with clinically positive neck nodes will have apparent involvement of retropharyngeal nodes, as demonstrated on computed tomography (CT) or magnetic resonance imaging (MRI). An 85% to 90% incidence of metastatic neck node disease exists, and about 50% have bilateral metastases.[17,32] The incidence of neck nodes does not correlate with T stage (see Chap. 6, Table 6-3). T4 lesions actually have a lower percentage of positive lymph nodes than do T1–3 lesions. Low-grade squamous cell carcinomas produce fewer metastases (73%) compared with high-grade carcinomas (92%).

The incidence of subclinical disease in neck lymphatics is difficult to estimate. The high-risk nodal groups (ie, retropharyngeal and junctional nodes) normally are included in the portals used to treat the primary lesion. Lee and associates[26] reported a series of 189 patients

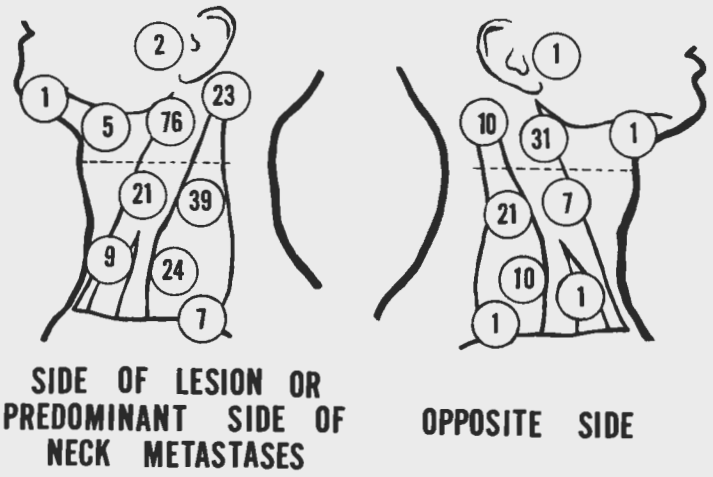

Figure 23-11. Distribution of metastases to lymph node areas in epithelial tumors of the nasopharynx. The circled numbers indicate the number of times the particular lymph node is involved. Note the high incidence of involvement of the lymph nodes of the spinal accessory chain. Total cases, 99. No lymph nodes were involved in 10 patients (10%); lymph nodes were involved in 89 patients (90%). There was unilateral involvement in 38 patients (38%), and bilateral involvement in 51 patients (52%). (Fletcher GH, Million RR. Malignant tumors of the nasopharynx. Am J Roentgenol Radium Ther Nucl Med 1965;93:47. Copyright © 1965, American Roentgen Ray Society)

with Ho stage I lesions (American Joint Committee on Cancer [AJCC] stage I and II) treated with irradiation to the primary lesions without elective irradiation to the clinically negative neck, although it is virtually impossible to miss the retropharyngeal and, probably, the junctional lymph nodes. Fifty-seven patients (30%) subsequently developed recurrent disease in the neck. The overall risk of subclinical disease in all patients with a clinically negative neck is probably in the vicinity of 70%.

Metastases to submental and occipital nodes appear only when a blockage of the common lymphatic pathways occurs, either by massive neck disease or by an untimely neck dissection.

Distant Metastasis

The incidence of distant metastasis at diagnosis in North American patients is 3%.[34]

The overall incidence of metastasis is approximately 35% to 40% and increases with advanced stages of disease.[1] Ahmad and Stefani[1] reported that 98% of distant metastases appear within 3 years of treatment and that the most common sites of involvement include lung, bone, and liver.

CLINICAL PICTURE

The most common presenting complaint is a painless upper neck mass or masses, which may be large when first discovered.[35] The neck mass may enlarge rapidly owing to necrosis or hemorrhage. Rarely, patients report exquisite tenderness and are unable to tolerate palpation of the masses.

Nasal obstruction and epistaxis are common. Decreased hearing and tinnitus due to otitis media are caused by obstruction of the eustachian tube. Unilateral otitis media is an uncommon diagnosis in adults, and should always lead to a thorough examination for tumor. Sore throat occurs in about 15% of patients, and is related to spread along the oropharyngeal wall. Facial pain may be referred from any of the three divisions of the trigeminal nerve. Occipital or temporal headache is seen frequently. Pain in the scalp over the mastoid area may be related to involvement of a high jugular lymph node that has become fixed to the skull and spine.

Pain initiated by lifting the head and extending the neck is related to posterior infiltration of the prevertebral muscles or retropharyngeal lymph nodes. Ballantyne[4] reported that lateral retropharyngeal lymph nodes involved by carcinoma produced a syndrome of pain, often severe and difficult to pinpoint. The pain is usually referred to the ipsilateral neck and ear, head, forehead, and orbit; it may be associated with a stiff neck or pain on extension of the neck.

Proptosis occurs with posterior orbital invasion, and usually displaces the eyeball straight forward. Trismus is related to the invasion of the pterygoid region.

Neurologic symptoms and signs occur in about 25% of patients. Any involvement of cranial nerves II through VI indicates intracranial extension into the cavernous sinus and pituitary region. Cranial nerves IX through XII and the sympathetic chain are involved in the poststyloid parapharyngeal space. Neel[34] reported a series of 151 patients with nasopharyngeal carcinoma in which 30 patients (20%) had cranial nerve involvement. The nerves involved were as follows: III (3), IV (3), V (22), VI (13), VII (3), VIII (3), IX (4), X (4), XI (1), XII (6), and the sympathetic chain (3).

The signs or symptoms in a series of 151 patients at the Mayo Clinic (Rochester, MN) were as follows[34]: neck mass (60%), ear plugging or fullness (41%), hearing loss (37%), epistaxis (30%), nasal obstruction (29%), headache (16%), ear pain (14%), neck pain (13%), and weight loss (10%).

Physical Examination

Fiberoptic nasoscopes and laryngoscopes are great aids in examining the nasopharynx. Early lesions occur on the lateral wall or roof; the nasopharyngeal surface of the soft palate is almost never the site of origin, and is not often invaded secondarily, even by advanced lesions. In early lesions the findings may be subtle: only slight fullness in the fossa of Rosenmüller, or a small submucosal bulge or asymmetry in the roof. Lymphomas and minor salivary gland tumors tend to remain submucosal until large.

Nasoscopy may show tumor growing into the poste-

rior and superior nasal cavity. Tumor may be seen infiltrating submucosally along the posterior tonsillar pillars, and occasionally down the posterior pharyngeal wall.

The cranial nerves should be carefully evaluated; the fifth and sixth cranial nerves are most commonly involved. The eyes should be measured for proptosis. Ear examination may show findings of otitis media and decreased hearing.

The clinical appreciation of enlarged retropharyngeal nodes requires both visualization and palpation of the high posterolateral pharyngeal wall, but the diagnosis is rarely made without the aid of CT or MRI. Marked retropharyngeal lymph node enlargement, such as occurs in lymphoma, distorts the posterior tonsillar pillar, shifting it medially and anteriorly. Such a mass may be misdiagnosed as a peritonsillar abscess, followed by an inappropriate incision and drainage procedure. The enlarged lymph nodes said to be classic for nasopharyngeal carcinoma are the junctional lymph nodes (see Chap. 6). When enlarged, these nodes bulge the sternocleidomastoid muscle just below the tip of the mastoid and may distort the earlobe. These lymph nodes lie in juxtaposition to the base of the skull and to the internal jugular vein as it exits from the jugular foramen.

METHODS OF DIAGNOSIS AND STAGING

Nasopharyngoscopy and Biopsy

Adults with large, visible masses should have a biopsy performed in the outpatient clinic. After the administration of a local anesthetic, a straight biopsy forceps is placed through the nose and the procedure is visualized indirectly from the nasopharynx; or a curved biopsy forceps may be inserted behind the retracted soft palate, and biopsy is directed by nasoscopic visualization. Biopsy of a small lesion and random biopsies require administration of general anesthesia; the palate is retracted with a Yankauer speculum, providing direct visualization of the nasopharynx. Since some of these lesions tend to grow submucosally, random biopsies must be deep to detect an invisible lesion. A mucosal sample is taken, and then the biopsy forceps is replaced in the biopsy site to obtain a deeper sample. If a juvenile angiofibroma is suggested, imaging with contrast should precede biopsy. In the proper clinical setting, a *typical* CT or MR appearance of a juvenile angiofibroma confirmed by angiography may be considered equivalent to a biopsy (see Chap. 24). When a carcinoma of the nasopharynx is suggested, but is not found on outpatient examination, a CT or MR scan should be done to help locate a tumor mass *before* examination under anesthesia and biopsy (see Chap. 15). Additionally, an occult nasopharyngeal carcinoma may be diagnosed by subjecting tissue obtained from fine-needle aspiration of a neck node to a polymerase chain reaction to detect the presence of the viral genome of the EBV.[14]

Diagnostic Imaging

Imaging is required for staging and treatment planning in all nasopharyngeal malignancies. In patients with suggested, but unconfirmed, nasopharyngeal cancer, CT or MRI is an essential part of the diagnostic process, and should be done before biopsy.

MRI is the preferred primary examination for disease in the nasopharynx, parapharyngeal space, and infratemporal fossa. Complementary CT is used in about 25% to 30% of patients. For skull base disease, MRI and CT both are used in the majority of cases. The necessity of using both depends on the pathologic process, the need to assess bone detail, and quality or availability of the MRI (see Chap. 4).

Technique of Examination

The high-resolution CT and MRI techniques described in Chapter 4 are required in the nasopharynx. Section thickness should always be 3 to 4 mm or less; 1- to 2-mm sections sometimes are used in a focused study of areas suspicious for early bone erosion. Intravenous contrast is always used, except when CT is being done *only* to look for skull base erosion. CT sections through the skull base should be processed using a soft tissue *and* bone algorithm. Axial *and* coronal sections should be done, regardless of whether CT or MRI is the primary examination tool. Sagittal images frequently are helpful in treatment planning and easy to do if MRI is used.

The neck is always included when CT is performed. It is considered optional for MRI, since it adds considerable time and complexity to the examination, as well as almost doubling the cost in some institutions.

Imaging for distant metastases includes a chest roentgenogram. Chest CT to include the liver and a bone scan are obtained only if patients have a clinical picture suggesting the presence of distant metastases.

Imaging of the Normal Anatomy

The normal anatomy of the nasopharynx, as seen on MRI, is shown in Figures 23-12 and 23-13.[30] Most diagnostic errors occur as a result of over-interpretation of variations in the surface contours of the nasopharynx and lack of appreciation of deep-tissue planes. The superficial appearance of the nasopharynx varies greatly with age. This variation is mainly related to the amount of lymphoid tissue present and bulk and tone of the pharyngeal and masticatory muscles. Pitfalls related to variations in the lymphoid tissue of Waldeyer's ring are also discussed in detail in Chapters 16 and 17.

SUPERFICIAL STRUCTURES. The superficial landmarks in the nasopharynx, including the torus tubarius, eustachian auditory tube orifice, and fossa of Rosenmüller (lateral pharyngeal recess) are often asymmetric in appearance. Most of the variation in the superficial contours of the nasopharynx is related to deposits of lymphoid tissue, which tends to atrophy with age. Lymphoid tissue is visualized better on MRI than with CT, and *always* remains superficial to the pharyngobasilar fascia and pharyngeal musculature. Both neoplastic and inflammatory conditions can lead to localized mass effect or infiltrative patterns. The most disconcerting finding caused by adenoid tissue is variation in the amount of air within the fossa of Rosenmüller; this is almost always a normal variant if the mucosa appears benign on physical examination, and no deeply infiltrating mass is seen on the imaging study. Lymphoid tissue within the nasopharynx will enhance moderately with either intravenous iodinated or paramagnetic contrast. Small, clini-

cally insignificant fluid areas will frequently be visible within the adenoidal pad; these are usually located near the roof of the nasopharynx and may be postinflammatory cysts, fluid within the pharyngeal bursa, or small remnants of Rathke's cleft.

With aging, the eustachian tube orifices appear more patulous, and the tori are smaller and somewhat better defined. The lateral pharyngeal recesses may become deeper or wider, and their area of contact with the skull base along the inferior petrous apex can be more fully appreciated.

DEEP ANATOMY. The dividing line between the pharynx and deeper tissue spaces is the pharyngobasilar fascia and the pharyngeal musculature; the retropharyngeal space lies between the nasopharyngeal wall and the prevertebral fascia. The parapharyngeal space lies laterally and is subdivided by the muscle bundles arising from the styloid process into its prestyloid and poststyloid components. The spaces are visible on CT and MRI because they contain fat; the sizes of the spaces vary considerably in different individuals. The paired prestyloid parapharyngeal spaces and pharyngeal muscles are always symmetric at the level of the nasopharynx. *A disease process obliterating the parapharyngeal space should be considered neoplastic until proven otherwise.* The pharyngeal musculature is easier to see on MRI than CT; the pharyngobasilar fascia can only be seen distinctly on MRI. Invasion of the fascia or muscle is a sign of aggressive disease, but can be subtle, and is not as sure an indicator of cancer as is parapharyngeal space invasion.

The carotid artery and jugular veins should always be clearly visible in the poststyloid parapharyngeal space, along with at least some surrounding fat. The intervening cranial nerves (IX through XII and the sympathetic chain) can sometimes be seen on high-resolution MRI. The retropharyngeal lymph nodes are almost always visible on MRI medial to the carotid artery at the border between the poststyloid parapharyngeal and retropharyngeal spaces; their signal intensity is the same as that of the normal lymphoid tissue lining the mucosa (see Chaps. 4 and 6). The nodes are normally no more than 3 to 5 mm in size in adults, but frequently measure up to 10 to 15 mm in infants and young children. The retropharyngeal nodes are more difficult to discern from the surrounding muscles and vessels on CT.

SKULL BASE AND CRANIAL NERVES. Whereas high-resolution CT provides the best possible images of the skull base, definitive imaging of the skull base can be accomplished with a good-quality MRI technique in many cases. The MRI visualization of the bone will depend on the amount of fatty marrow present, as well as the absence of signal from its cortical component.

The clivus and basisphenoid make up the posterior wall and roof of the nasopharynx, and are the foundation of the central skull base and cavernous sinus; the bony portion of the eustachian tube lies immediately lateral to the carotid canal. These anatomic relationships are best appreciated on coronal and sagittal MRI.

The fifth nerve ganglion, which lies within the cerebrospinal fluid-filled Meckel's cave, and its branches both within and outside the cavernous sinus are easily recognized on good-quality MRI and CT. The second and third divisions of the trigeminal nerve, which exit the skull base through the foramen rotundum and ovale, are visible on good-quality MRI (Fig. 23-14). The third, fourth, and sixth cranial nerves, along with the first division of the trigeminal nerve, are best visualized on coronal MRI as they course through and in the wall of the cavernous sinus. The cavernous segment of the carotid artery is seen by virtue of its low signal intensity on standard spin-echo MRI. On CT, the enhanced internal carotid artery is usually indistinguishable from the enhancement within the venous spaces of the cavernous sinus.

The jugular fossa, which lies just posterior to the carotid foramen, is usually larger on the right side. The jugular spur, which separates the pars nervosa from the pars venosum of the fossa, is variably visible because it may be either a fibrous or bony structure. Cranial nerve IX lies within the pars nervosa of the jugular fossa, whereas cranial nerves X through XII lie within the pars venosum along with the jugular vein. Normal variants include areas of dehiscence between the carotid canal and jugular fossa where they abut the middle ear cavity, and a high jugular bulb. The base of the pterygoid plates is part of the basisphenoid; the pterygopalatine fossa lies between the pterygoid processes and the maxillary antrum, and is contiguous with the inferior orbital fissure superiorly and the infratemporal fossa laterally. The foramen rotundum may be seen just above the base of the pterygoid plates. The second division of the trigeminal nerve passes through the upper portion of the pterygopalatine fossa as it courses toward the inferior orbital fissure and eventually the infraorbital groove and canal. The fat within these spaces is normally symmetric, although the size of vessels coursing through the spaces may vary slightly; obliteration of fat is a reliable sign of pathologic involvement.

The basisphenoid, which also forms the floor of the middle cranial fossa, and the styloid process serve as the attachment for most of the upper pharyngeal musculature. The attachments of the levator and tensor veli palatini muscles are visualized along the inferior petrous apex and basisphenoid, respectively. The third division of the trigeminal nerve often can be seen on MRI exiting the foramen ovale, just lateral to the attachment of the tensor veli palatini muscle, to course for a short distance adjacent to the upper parapharyngeal space, and then deflect laterally to travel within the masticator space and on to the mandible. Perineural enhancement within the cranial nerve exit foramina and prominent enhancement of venous plexuses just below the skull base are common normal variants (see Fig. 23-14).

Indications for Study

The uses for imaging in known or suspected nasopharyngeal cancer are as follows.

KNOWN NASOPHARYNGEAL CANCER. MRI is preferred as the primary examination for nasopharyngeal malignancies. Its multiplanar capability is particularly useful for showing the relationship of malignant tumors to the skull base, cavernous sinus, brain, orbits, and sinonasal region (Fig. 23-15). Its superior contrast resolution permits detection of subtle spread in deep tissues and distinction of obstructive versus tumoral disease in the sinuses and temporal bone.

Staging of the nodal metastases by imaging is less critical for nasopharyngeal carcinoma than in primary carcinomas of other upper aerodigestive tract sites, because the neck nodes are almost always involved. The

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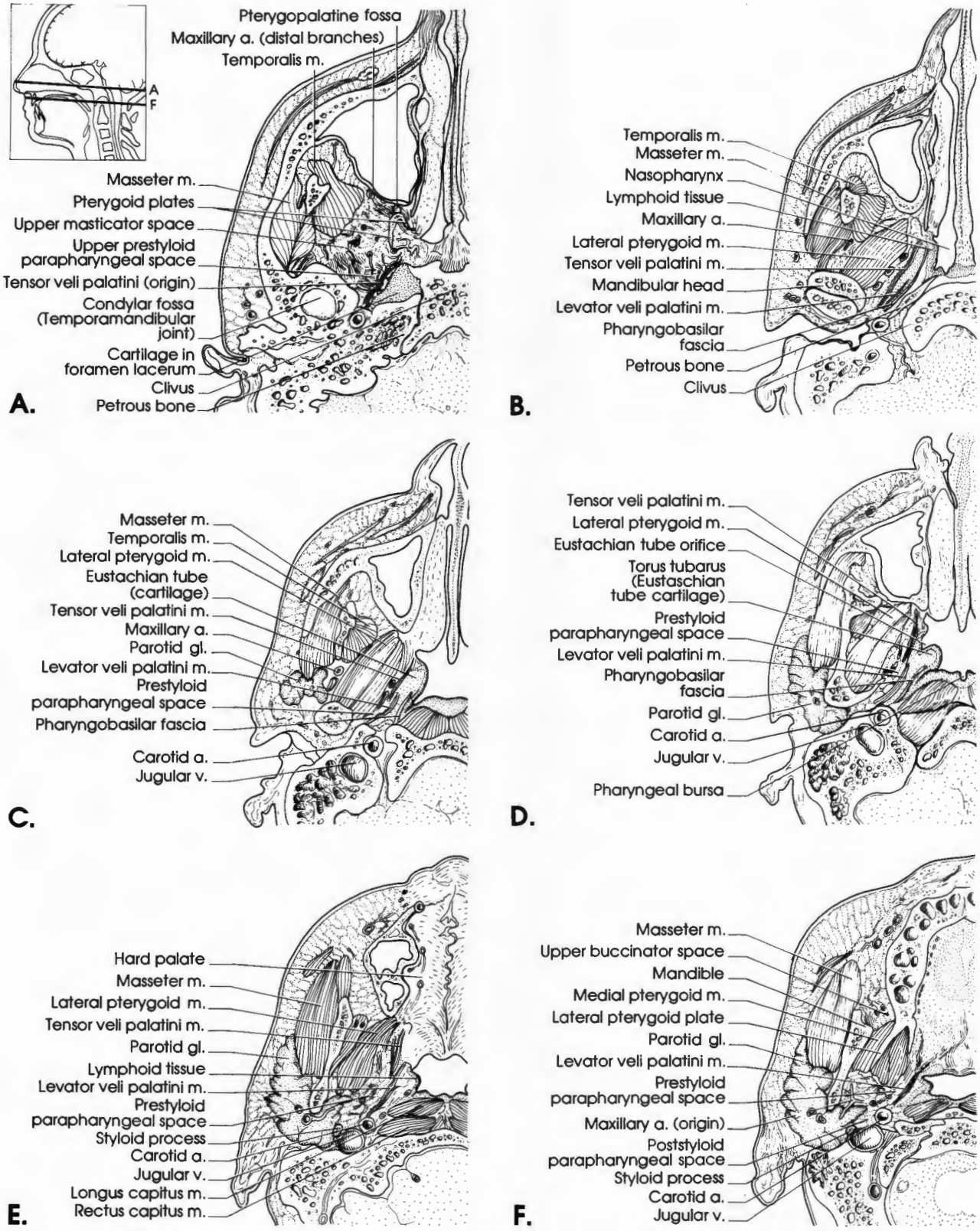

Figure 23-12. (*A* through *F*) Anatomic line diagrams from the skull base to the lower nasopharynx to correlate with accompanying MR images at the same levels in Figure 23-13. (Mancuso AA, Harnsberger HR, Dillon WP. Workbook for MRI and CT of the head and neck, ed 2. Baltimore, Williams & Wilkins, 1989:132–133)

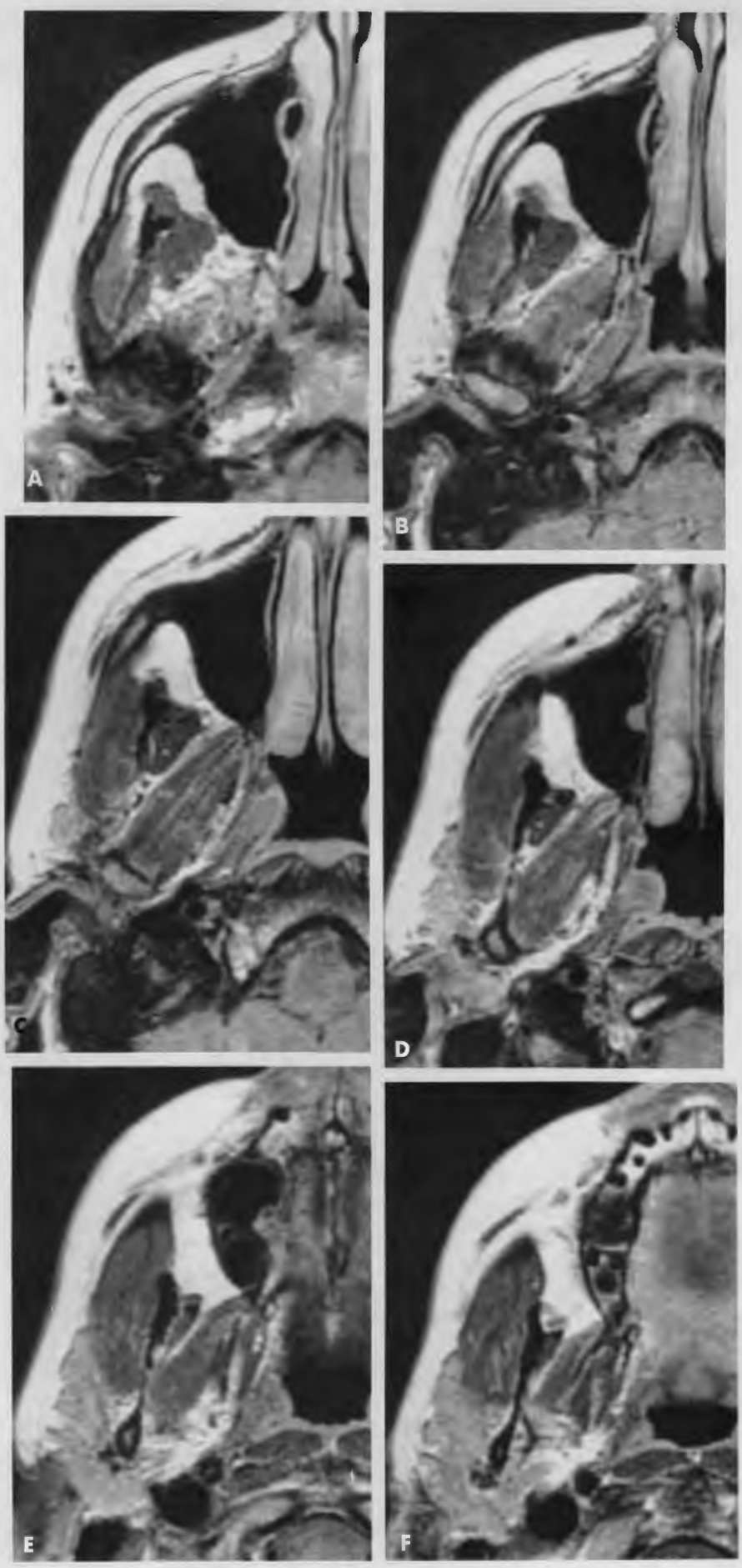

Figure 23-13. MR images to correlate with anatomic line diagrams from the skull case to the inferior margin of the nasopharynx shown in Figure 23-12. (Mancuso AA, Harnsberger HR, Dillon WP. Workbook for MRI and CT of the head and neck, ed 2. Baltimore, Williams & Wilkins, 1989;132–133)

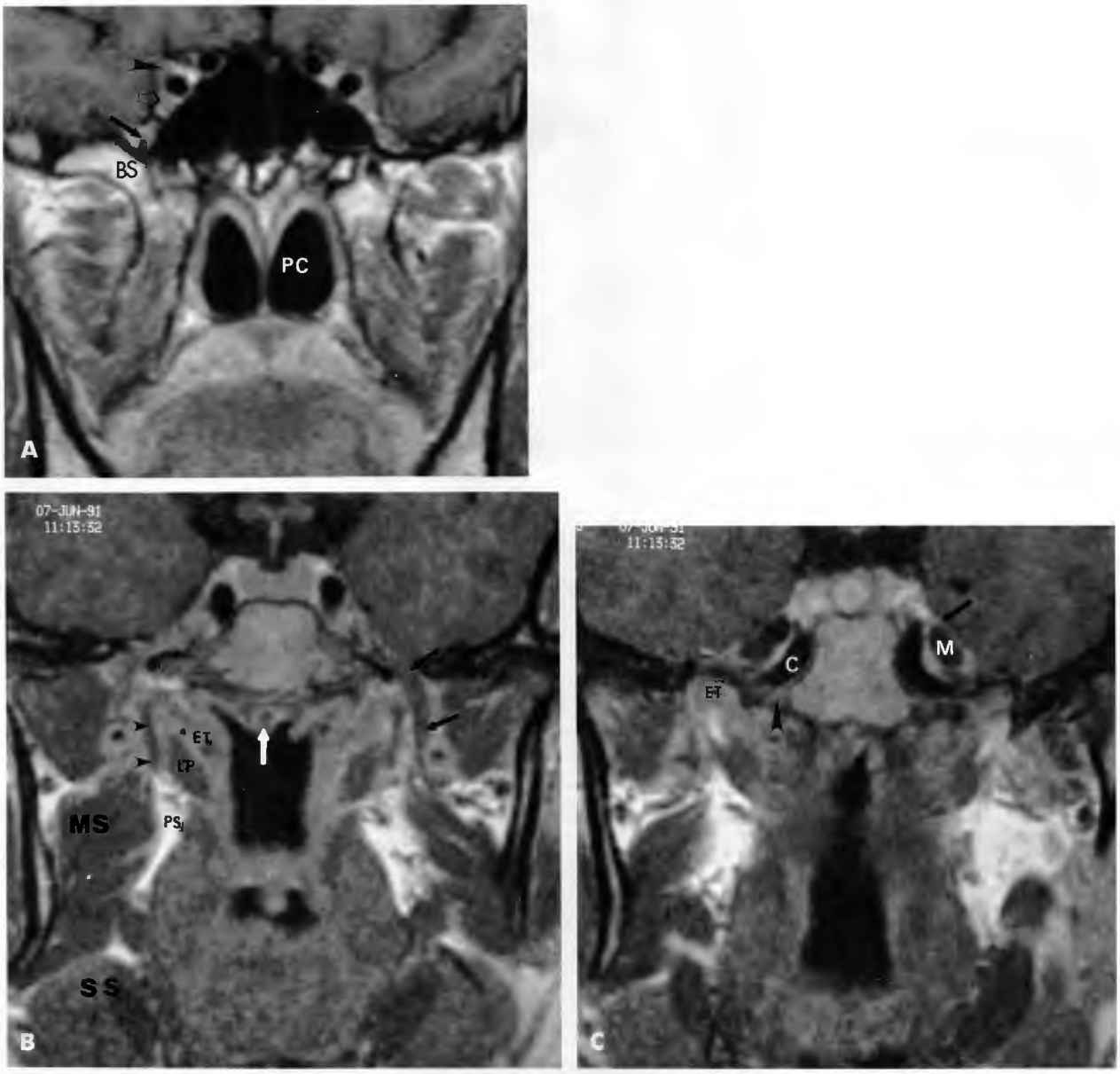

Figure 23-14. Coronal MRI through the nasopharynx, central skull base, and cavernous sinus shown from the most anterior section (*A*) to the most posterior (*C*). (*A*) A section made through the posterior choana (PC) at the junction of the nasopharynx and oropharynx. The basisphenoid (BS), at this point, joins the pterygoid process and forms the floor of the middle cranial fossa. The maxillary nerve (*arrow*) is seen in the cranial end of the foramen rotundum. Cranial nerves III (*arrowhead*), IV, and VI and first division of the trigeminal nerve (*open arrow*) also are visible. (*B*) The section through the midnasopharynx shows the mandibular nerve exiting the skull base through the foramen ovale (*arrows*). The eustachian tube (ET) is traveling obliquely toward the skull base just superior to the levator veli palatini muscle (LP) and medial to the tensor veli palatini muscle (*arrowheads*). Lymphoid tissue lines the roof of the nasopharynx (*white arrow*). Note how the fat within the prestyloid parapharyngeal space (PS) separates the masticator space musculature (MS) from the pharyngeal wall musculature. The parapharyngeal space is continuous from the skull base lying adjacent to both the nasopharynx and oropharynx to its termination in the submandibular space (SS). (*C*) A section made through the posterior aspect of the nasopharynx. The eustachian tube (ET) travels toward the hypotympanum adjacent to the carotid artery (C) in its carotid canal. The cavernous sinus surrounds Meckel's cave (*arrow*) at this point. The trigeminal ganglion lies within Meckel's cave (M), which is also known as the cistern to the trigeminal ganglion. Cartilage fills the foramen lacerum region just below the carotid artery (*arrowhead*). Again, note the relationships of the parapharyngeal space described in *B*.

advantage of CT over MRI in staging neck disease (see Chap. 6) becomes less critical because of this factor.

SUSPECTED OCCULT NASOPHARYNGEAL MALIGNANCY. Patients with cervical lymph node metastases from an unknown primary (see Chap. 15), persistent unilateral serous otitis media despite adequate management, or cranial nerve deficits possibly attributable to nasopharyngeal cancer should be studied as described in Chapter 4, and in this chapter.

SUBMUCOSAL NASOPHARYNGEAL (AND OROPHARYNGEAL) MASSES OF UNCERTAIN ETIOLOGY. Patients with submucosal masses in the nasopharynx should *always* be studied before biopsy. Such masses are frequently of parapharyngeal rather than nasopharyngeal origin. Imaging will often identify the cause of the mass; however, even if the diagnosis is not certain, imaging will suggest the next best course of action and may help avoid biopsy of an abnormal vessel (eg, tortuous or aneurysmal carotid artery) or vascular mass (eg, paraganglioma), or transmucosal, incisional biopsy of a parapharyngeal benign mixed tumor (Fig. 23-16).

POSSIBLE RECURRENCE OF NASOPHARYNGEAL CANCER. MRI is preferred over CT. This is discussed more completely in a following section on diagnosis and management of recurrence.

SUSPECTED JUVENILE ANGIOFIBROMA. For further information, see Chapter 24.

Staging

The AJCC staging system for nasopharyngeal primary tumors is listed below[2]:

Tis:	Carcinoma in situ
T1:	Tumor confined to one subsite of nasopharynx
T2:	Tumor invades more than one subsite of nasopharynx
T3:	Tumor invades nasal cavity and/or oropharynx
T4:	Tumor invades skull and/or cranial nerve(s)

Baseline and periodic posttreatment eye evaluation is recommended when the orbits are partially irradiated. Baseline hearing tests may be useful in that insurance companies may not reimburse patients for management of posttreatment hearing disorders unless these are shown to be secondary to the tumor or the irradiation.

TREATMENT

Factors in the Selection of Treatment

The treatment of most malignancies of the nasopharynx is radiation therapy by default, since surgical resection usually is not appropriate. Although skull base surgery has rendered possible the excision of nasopharyngeal carcinoma, surgery is reserved for patients with a resectable local recurrence after a course of radical irradiation. Occasionally, a small adenocarcinoma or sarcoma may be locally excised. Neck dissection is used less often in the management of neck disease in nasopharyngeal cancer compared with other sites because of the good success rate with radiation therapy alone; the high incidence of bilateral nodes; the frequent involvement of the junctional and retropharyngeal lymph nodes, which are not entirely removed by neck dissection; and the multiplicity of nodes, which usually predicts a higher failure rate with surgery. We have added neck dissection more often in recent years, however, particularly in patients with one, or perhaps two, large masses. Although large masses sometimes can be controlled by radiation therapy alone, the large doses produce significant, persistent fibrosis. The addition of a neck dissection in place of an extra 1500 to 2000 cGy will produce less fibrosis in later years and improve neck control rates. Neck dissection should also be recommended for persistence or recurrence after radiation therapy.

The role of adjuvant chemotherapy is controversial. Dimery and colleagues,[12] from M. D. Anderson Hospital (Houston), reported significantly improved local–regional control and survival rates in a series of 34 patients with stage IV nasopharyngeal carcinoma who received adjuvant chemotherapy, compared with 69 nonrandomized control patients treated with radiation therapy alone. There was no difference in the incidence of distant metastasis. The use of bleomycin sometimes resulted in severe neck fibrosis. In contrast, Tannock and coworkers,[42] from Princess Margaret Hospital (Toronto), reported no improvement in absolute and disease-free survival rates in a series of 51 patients treated with two cycles of methotrexate, bleomycin, and cisplatin followed by radiation therapy, compared with 140 matched historical controls treated with radiation therapy alone. Rossi and associates[39] reported a randomized trial comparing radiotherapy alone (116 patients) with radiotherapy followed by six monthly cycles of vincristine, cyclophosphamide, and doxorubicin (113 patients). No difference occurred in relapse-free survival or overall survival at 4 years; the pattern of relapse also was similar in the two treatment groups. Use of adjuvant chemotherapy for local–regional nasopharyngeal cancer should be regarded as investigational.[21]

Irradiation Technique

The anatomic planning is the same for the various grades of squamous cell carcinoma, the transitional cell carcinoma, and the lymphoepithelioma. Recommended doses are summarized in Table 23-2. Because of the large treatment volume, patients often are treated initially with 180 cGy per fraction, one fraction per day, 5 days a week; the dose per fraction may be increased to 200 cGy for the reduced portals. Some patients from the University of Florida are treated with twice-a-day fractionation at 110 to 120 cGy per fraction and a minimum 6-hour interval between treatments. All patients are treated with continuous-course irradiation.

The total dose to the primary lesion in children probably should be limited to 6000 cGy for T1–2 lesions and 6500 cGy for T3–4 cancers (dose specified for once-a-day fractionation, 180 cGy per fraction). Because almost all pediatric nasopharyngeal cancers are lymphoepitheliomas, those dose levels are consistent with the dose guidelines outlined in Table 23-2.[37]

Treatment Planning for T1, T2, and Early T3 Lesions

Small-volume irradiation should not be given, even for an early epithelial tumor of the nasopharynx. If, after

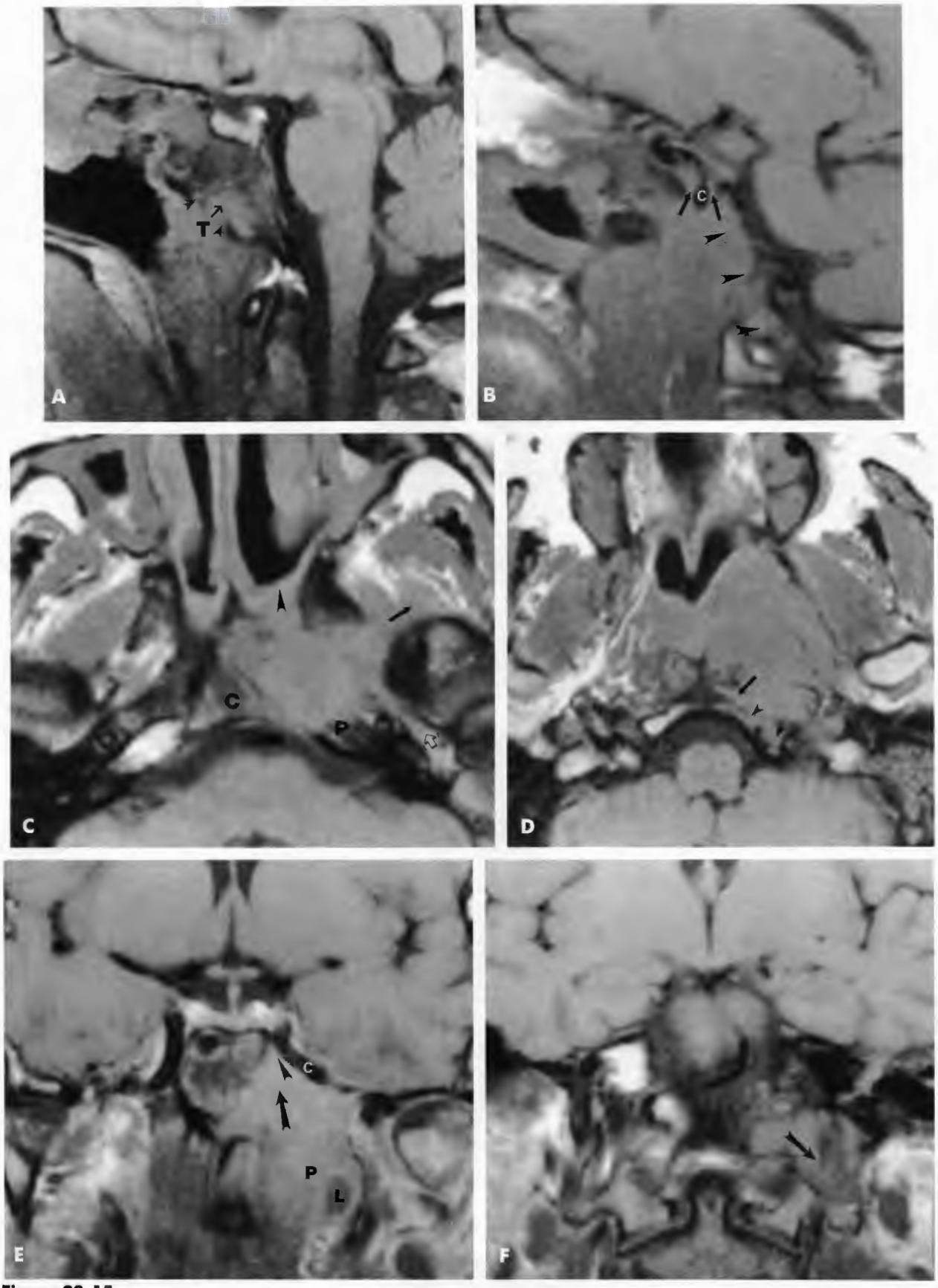

Figure 23-15.

TABLE 23-2. Guide to Dosage* for Primary Nasopharynx Tumors†

Stage	Fractionation Schedule	Squamous Cell Carcinoma (cGy)	Lymphoepithelioma (cGy)
T1, T2, early T3	1 per d	6500	6000
	2 per d	7440	6900
Late T3, T4	1 per d	7000	6500
	2 per d	7680	7200

* 900 cGy per week. A boost to the base of skull and nasopharynx is added to the basic dose listed below. See the text for details.
† See Chap. 34 for additional information.
(Adapted from Fletcher GH, Million RR. Nasopharynx. In: Fletcher GH, ed. Textbook of radiotherapy, ed 3. Philadelphia, Lea & Febiger, 1980:371)

complete clinical and imaging workup, the tumor is thought to be limited to the nasopharynx (T1 or T2) or to have minimal soft tissue extension (early T3), the following areas are included in the initial treatment volume:

- Nasopharynx proper
- Posterior 2 cm of the nasal cavity
- Posterior ethmoid sinuses
- Entire sphenoid sinus and basioccipital bone
- Cavernous venous sinus
- Base of skull (7- to 8-cm width encompassing the foramen ovale, carotid canal, and foramen spinosum)
- Pterygoid fossae
- Posterior one fourth of the orbit
- Posterior one third of the maxillary sinus
- Lateral and posterior oropharyngeal wall
- Retropharyngeal nodes
- Neck lymph nodes above the thyroid notch

Historically, a four-field arrangement with cobalt-60 (^{60}Co) has been used at this institution for T1, T2, and early T3 lesions. The advantage of this technique, compared with parallel-opposed lateral fields, is that the dose to the mandible, auditory structures, and pterygoid musculature is reduced, thus decreasing the risk of bone exposure, serous otitis media, and trismus. Although the four-field technique is at least as successful as the two- or three-field techniques, it is a difficult technique to teach; the set-up of the anterior fields is done anatomically, and port films are essentially useless. Additionally, with the availability of CT or MRI, nearly all patients are noted to have involved retropharyngeal nodes at the C1–2 level. Although these nodes lie near the inferior margin (mid tonsillar fossa) of the anterior oblique fields, recurrence in the retropharyngeal lymph nodes was rarely seen. In most centers, almost all patients are currently treated with opposed lateral fields, but this technique does not produce an ideal dose distribution if the nodes are clinically negative.

A four-field arrangement with ^{60}Co or 4- to 6-MV x-ray is depicted in Figure 23-17. The lateral fields deliver about two thirds and the facial fields about one third of the tumor dose.[18] The lateral fields are angled 5 degrees posteriorly to ensure adequate posterior margins while avoiding direct ipsilateral irradiation of the external and middle ear, and to reduce irradiation to the contralateral eye. A 5-degree posterior tilt shifts the field edge 8 mm backward at the midline. The anterior facial fields are angled medially 20 to 30 degrees. By using the collimator lights as shown in Figure 23-18, one can visualize the direction of the beam to determine the superior tilt and accurately reproduce the setup each day. The anterior facial fields with their inferior border at the level of the commissure of the lip provide adequate inferior coverage to about the level of the mid tonsillar fossa (angle of the mandible).

When only opposing lateral fields are used, a 6- to 20-MV beam improves the dose distribution, compared with ^{60}Co, and may be used for all or part of the treatment course, depending on the presence or absence of clinically positive lymph nodes (Fig. 23-19). The dimensions of the 90% isodose volume at the central axis for parallel opposed fields with a 5-degree posterior tilt for

◄ **Figure 23-15.** A patient with squamous cell carcinoma of the nasopharynx. (*A*) Sagittal MRI just off the midline demonstrates the cephalocaudal extent of the primary tumor (T) in the nasopharynx. Note the erosion of the clival cortex (*between the arrowheads*) and extension of the tumor through this bony defect into the clivus (*arrow*). (*B*) A sagittal section taken farther off the midline than that seen in *A* through a plane paralleling the cavernous sinus. Tumor (*arrows*) encases the carotid artery (C) as the artery courses through the cavernous sinus. The tumor fills the clivus, extending far inferiorly (*arrowheads*), suggesting the tumor could be found as far posteriorly and inferiorly as the occipital condyle. (*C*) Axial sections show the tumor invading the clivus (C) and inferior aspect of the petrous apex (P). The tumor spreads into the lateral pterygoid muscle (*arrow*) and toward the posterior aspect of the nasal cavity (*arrowhead*). Tumor is also growing into the bony portion of the eustachian tube; an interface can be seen between tumor and secondary obstructive disease in the middle ear (*open arrow*). (*D*) An axial section made at the level of the hard palate demonstrates tumor invading the prevertebral muscles (*arrow*) and continuing posteriorly and inferiorly to involve the lower clivus and the region of the hypoglossal canal (*arrowheads*). This particular extension resulted in a significant adjustment of the radiotherapy treatment plan. (*E*) The coronal section shows tumor invading the petroclival fissure and the region of the foramen lacerum (*arrow*). Note how the tumor follows the carotid artery (C) into the medial aspect of the cavernous sinus (*arrowhead*). This section also differentiates between the primary tumor (P) and the metastatic retropharyngeal node (L). (*F*) A coronal section made through the foramen magnum shows the tumor within the basisphenoid, basiocciput, and extending toward the occipital condyle (*arrow*). This posterior and inferior extension was not fully appreciated on CT. It was confirmed in two other planes (*B* and *D*) and resulted in a significant adjustment in the radiotherapy plan.

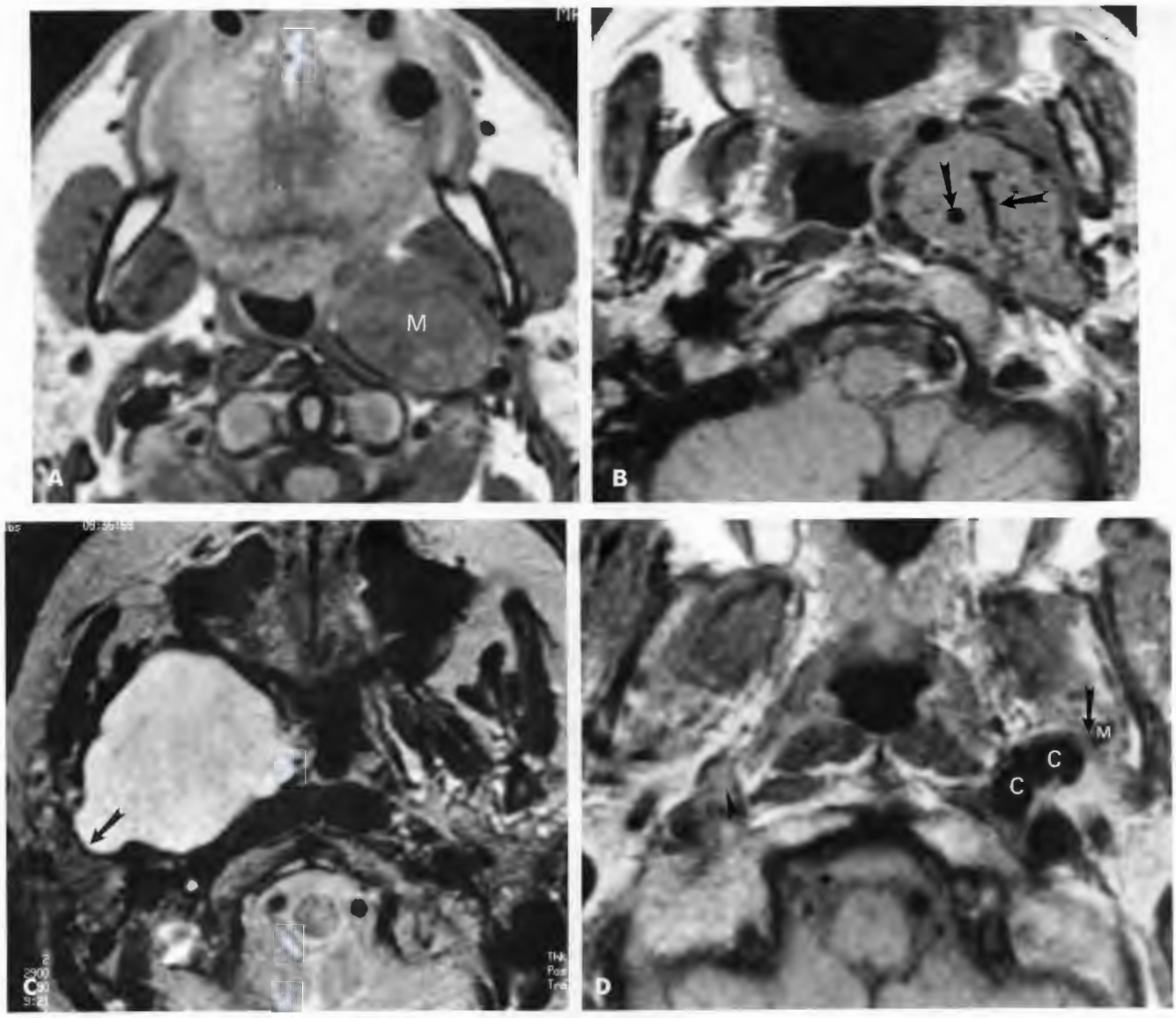

Figure 23-16. Views of four different lesions in the parapharyngeal space. All are MRI sections. (*A*) This patient had a submucosal bulge in the nasopharynx and oropharynx. This, and other sections, strongly suggestd the mass (M) to be a schwannoma arising in the poststyloid parapharyngeal space from the sympathetic trunk. This was confirmed surgically. (*B*) A middle-aged woman had a submucosal mass bulging the wall of the nasopharynx and oropharynx. This T1-weighted MR image shows the mass with very large vessels (*arrows*) in its interstices. The mass arises in the poststyloid parapharyngeal space. The combination of findings is virtually diagnostic of a glomus vagale type of paraganglioma arising in the poststyloid parapharyngeal space. This was confirmed angiographically. The patient elected to have radiation therapy; no biopsy specimen was obtained. (*C*) A middle-aged woman had a submucosal bulge involving the nasopharynx and oropharynx. This heavily T2-weighted axial image shows a very bright mass centered in the parapharyngeal space. This, and other images, strongly indicated that this was a benign mixed tumor arising in parapharyngeal space with secondary extension into the parotid space (*arrow*). These findings were confirmed surgically; no further diagnostic studies (ie, angiography or biopsy) were necessary. (*D*) This patient had trigeminal neuralgia in the distribution of the mandibular nerve. CT (not shown) was done before the placement of a radiofrequency lesion of the trigeminal nerve to relieve the patient's pain. CT revealed a mass in the prestyloid parapharyngeal space, which was believed to be either a lesion within that space, or an abnormality involving the carotid artery. The T1-weighted MRI shown here revealed a loop in the internal carotid artery (C) immediately adjacent to the expected course of the mandibular nerve (*arrow*). The mandibular nerve could be pressed between the tortuous carotid and the adjacent branches of the internal maxillary artery (M). The patient subsequently underwent the placement of radiofrequency lesion and the pain was relieved. An angiogram was not done since the remainder of the MRI sections showed that this was, in fact, a loop of the carotid rather than an aneurysm. The opposite carotid was occluded (*arrowhead*).

initial and reduced fields are shown in Figure 23-20 for various beam energies.

Local failures may be partly related to the administration of a lower dose than planned in the posterior and superior aspect of the nasopharynx and base of skull as a result of several factors:

Field edge effect: The posterior and superior aspect of the nasopharynx, the base of the skull, and the cavernous sinuses are on the edge or in the corner of the fields, and thus the dose is less than the dose at the central axis.

Bone: An almost continuous slab of dense bone occurs at the level of the base of the skull, and differential absorption occurs, even with high energies (for ^{60}Co, 3.5% per centimeter of bone).

Contour correction: The contour is usually taken at a level through the upper lip and the external auditory meatus; however, most patients are about 1 cm thicker at the level of the zygomatic arch, which causes an underdosage of about 5% from the lateral fields.

Field angulation: If the four-field technique is used, the anterior fields are angled superiorly, which is not allowed for in the contour; this adds about another centimeter that is not taken into consideration in the volume distribution of the anterior fields. Air in the sinuses and nasal cavity may partially compensate for this error.

A supplement of 500 cGy is added to the base of the skull and nasopharynx through 5 × 4-cm opposed lateral fields to make up for the underdosage (see Fig. 23-17*B*). Corrections for homogeneity with CT treatment planning and off-axis treatment plans through the base of the skull may assist in treatment planning.

Treatment Planning for Late T3 and T4 Lesions

BASE OF SKULL OR INTRACRANIAL NERVE INVOLVEMENT. Extension to the base of the skull or any involvement of cranial nerves II through VI requires that the superior border be raised to include all of the pituitary, the base of the brain in the suprasellar area, the adjacent middle cranial fossa, and the posterior portion of the anterior cranial fossa. A minimum dosage of 7000 cGy is planned in patients with T3 and T4 squamous cell carcinoma, and 6500 cGy is the minimum in those with lymphoepithelioma. The point of dose specification encompasses a volume that is 7 to 8 cm wide, and 4 to 5 cm anteroposteriorly. At the completion of the basic treatment a boost is added to the nasopharynx and the base of the skull with a reduced field to compensate for underdosage. A weekly dose of 900 cGy (once-a-day fractionation) may reduce the risk of late complications that may be encountered at 1000 cGy per week. With doses higher than 7000 cGy (once-a-day fractionation) severe central nervous system and optic nerve complications may occur. Extreme care in treatment planning must be used.

In recent years, twice-a-day fractionation has been used with continuous-course irradiation, 110 to 120 cGy per fraction, to total doses of 7440 cGy for T1–2 lesions and 7680 cGy for T3–4 cancers.

We have no experience with endocavitary therapy for previously untreated lesions.

ANTERIOR EXTENSION. In patients with anterior invasion of the orbit, ethmoids, or maxillary sinuses, a three-field treatment technique (opposed lateral fields and a single anterior field) may be employed. This technique is similar to that used for primary cancers of the nasal cavity and ethmoid sinuses (see Chap. 22). A three-field arrangement requires use of wedges on the lateral fields and partial use of wedges on the anterior field to produce a satisfactory volume distribution. The lacrimal gland should be shielded, if possible, to retain tears and help prevent development of a painful eye. When wedge fields are used on the lateral portals, it is not feasible to include the upper neck in the primary fields. The neck is then irradiated through anterior and posterior portals with photons or with lateral electron-beam portals to avoid overdose to the spinal cord. One such patient with an extensive destructive lesion of the base of skull and unilateral orbital involvement is living 7.5 years after treatment, free of disease.

Neck Nodes

A comprehensive en bloc plan must be developed to irradiate the neck to the level of the clavicles for both the epithelial lesions and the lymphomas. Patients with no palpable disease in the neck should have full neck irradiation.[6]

UPPER NECK. The retropharyngeal nodes are included in the treatment of the primary lesion (see Fig. 23-17*D*). The upper neck nodes are included in the lateral primary fields to the level of the thyroid notch. The posterior margin is placed 2 cm or more behind the upper border of the sternocleidomastoid to encompass the junctional and high spinal accessory nodes. The superior margin is 2 to 3 cm above the tip of the mastoid. The portals are extended anteriorly into the submental area only if disease occurs in the submandibular triangle, or if patients have had a neck dissection before irradiation.

If a four-field arrangement is used, the upper neck nodes usually have received 4000 to 5000 cGy when the treatment of the primary lesion is shifted to the anterior facial fields. If there was no palpable neck disease before treatment, further neck irradiation is not required. Portions of the neck that are clinically involved must have the dose raised to appropriate levels. If only photons are available, anterior and posterior neck fields are designed to shield the midline and protect the spinal cord. Wedges are used to improve the distribution (see Chap. 15, Fig. 15-4D). If electrons are available, they may be used to complete the neck treatment in suitable situations. An appropriate neck dissection should be considered.[9]

LOWER NECK. The lower neck is treated through an anterior portal with a shield over the larynx (see Chap. 6).

DOSAGE TO NODES. Guidelines for selecting the dosage, depending on the histologic type and size of nodes, are presented in Table 23-3. Large neck nodes from a lymphoepithelioma may be just barely palpable on a Monday after 400 to 500 cGy given the week before; conversely, they may, on occasion, still be palpable after 5000 cGy over 5 weeks.

Acute Sequelae

The large volume of mucosa that is irradiated produces unpleasant side effects during treatment. A sore throat begins at the end of the second week of therapy and per-

(text continues on page 621)

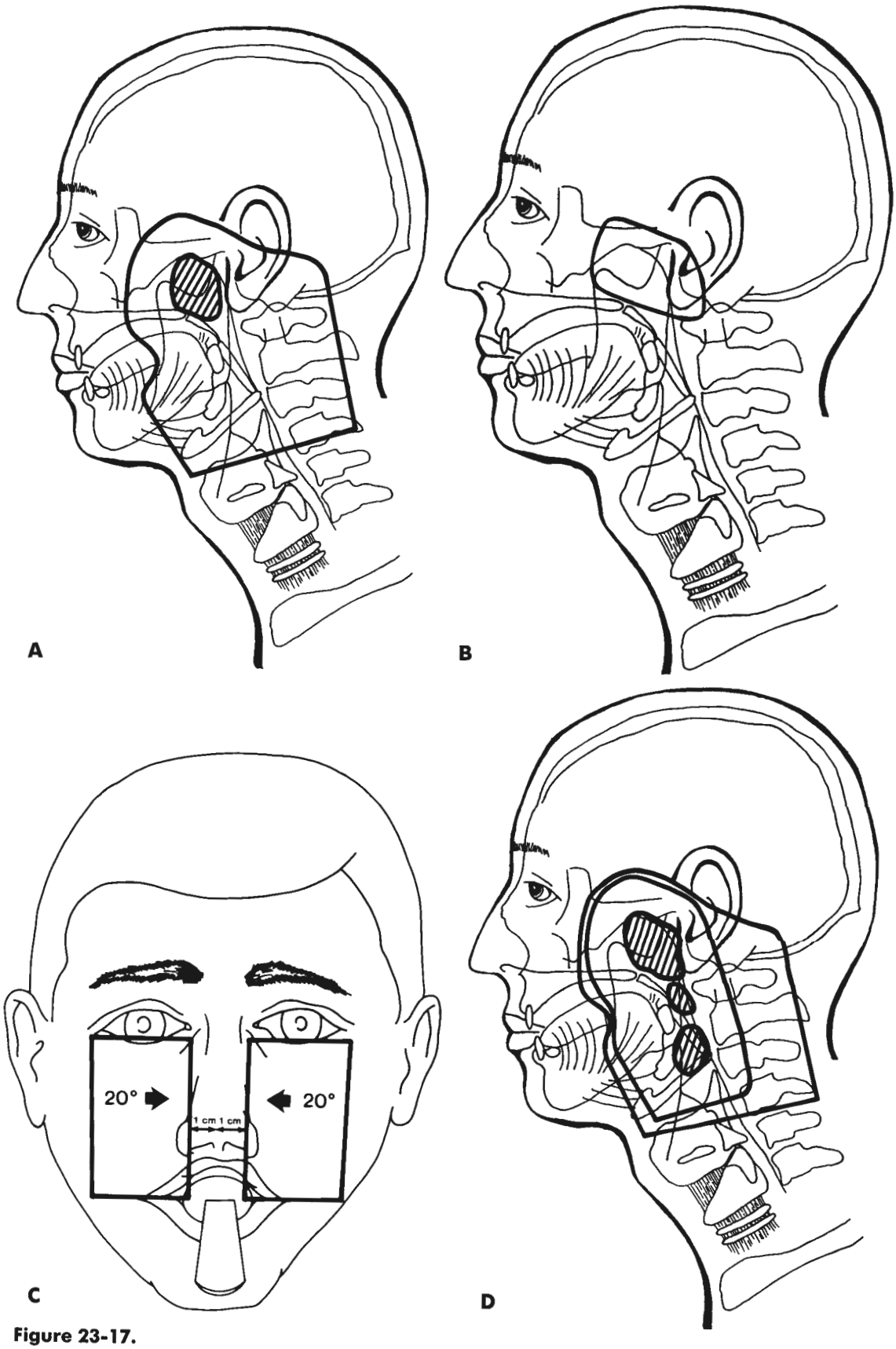

Figure 23-17.

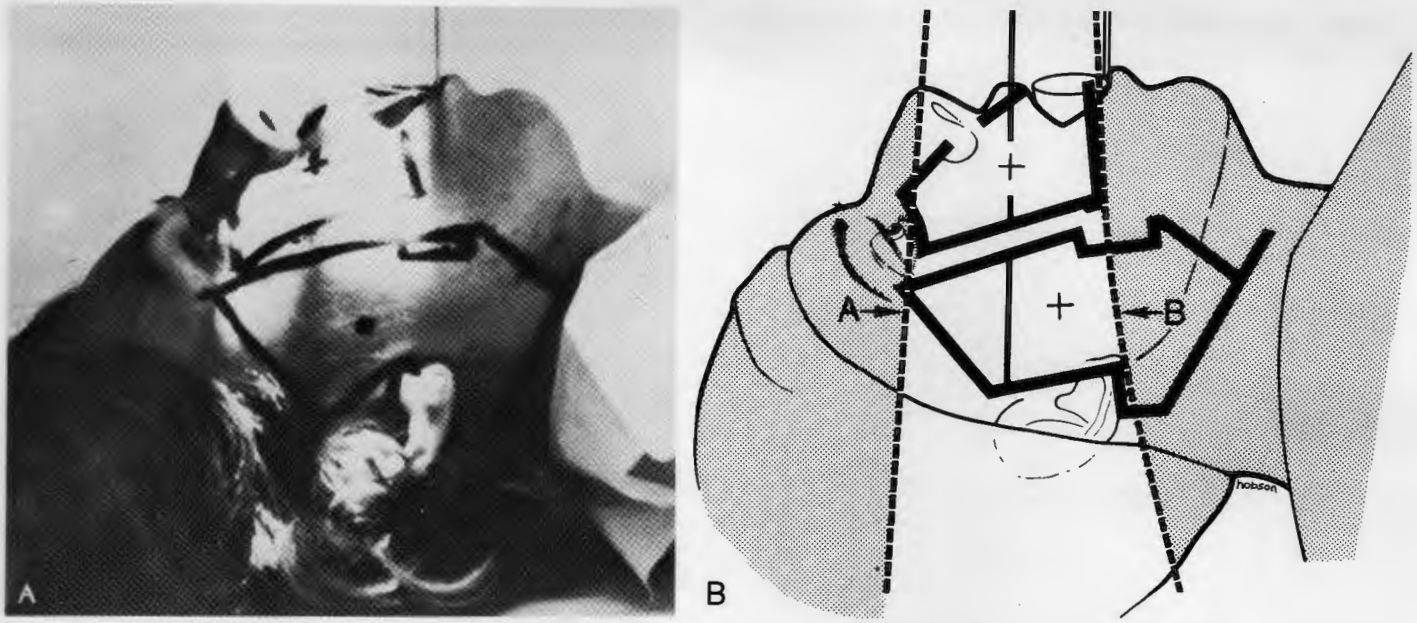

Figure 23-18. Tilted anterior treatment fields. (*A*) Use of collimator lights for setup. (*B*) Schematic of *A*. (Fletcher GH, Million RR. Nasopharynx. In: Fletcher GH, ed. Textbook of radiotherapy, ed 3. Philadelphia, Lea & Febiger, 1980:375)

TABLE 23-3. Guide to Dosage* for Neck Nodes

	Squamous Cell Carcinoma		Lymphoepithelioma	
	Minimum Tumor Dose (cGy)	Boost to Residual† (cGy)	Minimum Tumor Dose (cGy)	Boost to Residual† (cGy)
No palpable nodes	5000	—	4500	—
Small nodes (1–2 cm)	6000	500–1000	6000	500–1000
Nodes (3–5 cm)	6000	1500–2000	6000	1000–1500
Massive fixed nodes	6000	2000–3000	6000	1500–2000

* One fraction per d, usually 900 cGy to 1000 cGy per wk.

† Boost dose added through portal just covering palpable residual disease. Neck dissection may be substituted for radiotherapy boost in select cases (eg, grade 2 squamous cell carcinoma in a solitary 5-cm subdigastric node).

(Adapted from Fletcher GH, Million RR. Nasopharynx. In: Fletcher GH, ed. Textbook of Radiotherapy, ed 3. Philadelphia, Lea & Febiger, 1980:380)

◄ **Figure 23-17.** Portals for irradiation of the primary tumor. (*A*) The lateral portal is designed to treat the primary tumor (*shaded area*) with a 2- to 3-cm margin, as well as the retropharyngeal, upper internal jugular, and spinal accessory lymph nodes. The field may be enlarged to treat the submandibular nodes if extensive neck disease is present. The inferior margin of the portal is at the level of the thyroid notch. The beam is angled 5 degrees posteriorly, as determined by verification films. (*B*) The reduced portal for the boost to the base of the skull. The posterior and superior borders of the boost portal may be outside the original margins to ensure adequate compensation for the low dosage at the base of the skull. (C) Anterior portals. A cork and tongue blade are placed in the mouth to depress the tongue as far as possible out of the treatment fields. The beam is tilted medially on an average of 20 to 30 degrees. The beam is aimed superiorly with the aid of the collimator light, as shown in Figure 23-21. The superior margins glance the eyeballs. The medial margins usually are 1 cm from the midline. The inferior borders normally are at the commissure of the lip, and the fields usually are about 6 cm wide. The anterior fields are used infrequently because most patients have involved retropharyngeal nodes, as demonstrated on CT or MRI, that would be on the edge, or excluded from, those fields. (*D*) Example of initial and reduced lateral fields used to treat a nasopharyngeal cancer with involved retropharyngeal lymph nodes. (Shaded areas indicate tumor.)

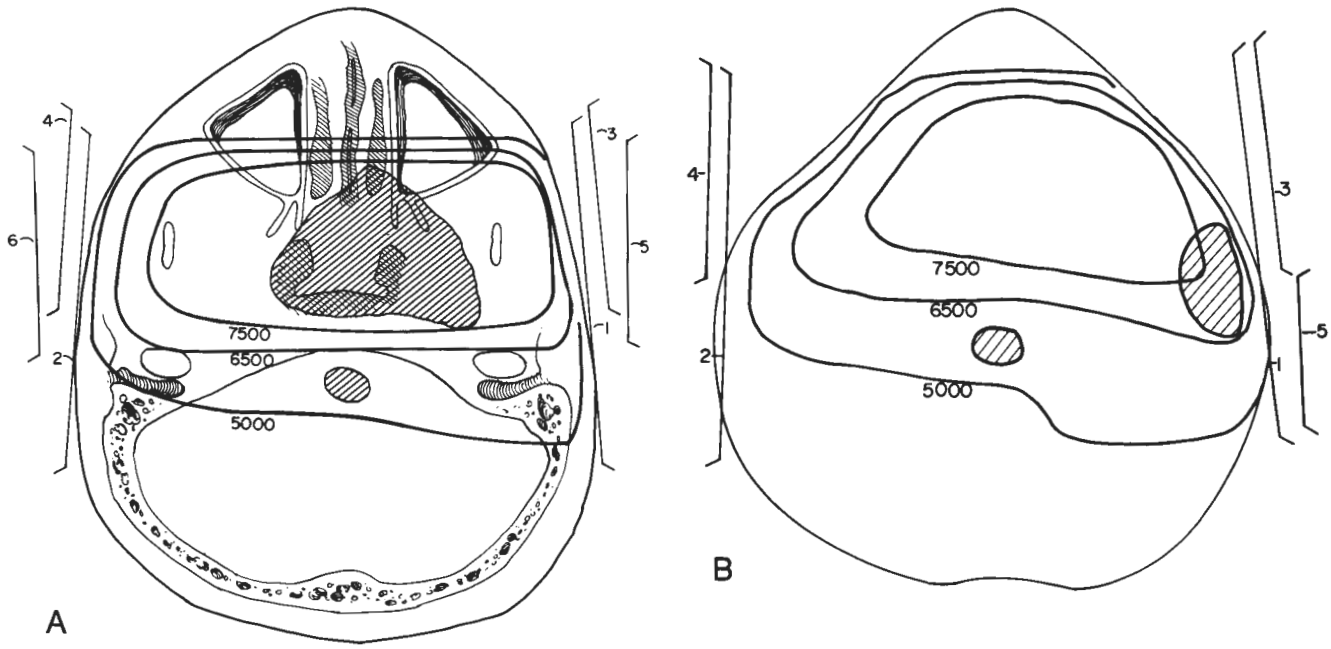

Figure 23-19. (*A*) Isodose distribution using only lateral portals for treatment of a carcinoma of the nasopharynx (*hatched lines*) with one right subdigastric lymph node. The initial 5000 cGy is given with a right lateral ^{60}Co beam (portal 1) and a left lateral 17-MV beam (portal 2). The spinal cord is shielded, and treatment is continued with 17-MV photons (portals 3 and 4) weighted 2 : 1 in favor of the right. Portals 1 through 4 are angled 5 degrees posteriorly. A boost of 500 cGy is added to the base of the skull with 17-MV photons to reduced portals (5 and 6). The uncorrected high-dose volume (7500 cGy) could be reduced by giving a small portion of the treatment from the anterior. The actual dose to the base of the skull in this instance is closer to 7000 cGy.

Portal	Energy	Field Size (cm)	Given dose (cGy)
1	^{60}Co	10 × 14	3220
2	17 MV	10 × 14	3220
3	17 MV	6 × 12	1934
4	17 MV	6 × 12	967
5	17 MV	6 × 4	456
6	17 MV	6 × 4	288

(*B*) Isodose distribution in the neck. The planned dose to the left neck is 4500 cGy to 5000 cGy for subclinical disease. The right neck lymph node is partially excluded from the reduced photon portals (portals 3 and 4) after approximately 5000 cGy. A 12-MeV electron portal is added on the right (portal 5). The final minimum dose to the right upper neck lymph node is 6500 cGy. The dose to the lymph node would be increased to 7000 cGy, with an appositional electron beam portal or with parallel opposed anterior and posterior portals with wedges.

Portal	Energy	Field Size (cm)	Given dose (cGy)
1	^{60}Co	10 × 14	3220
2	17 MV	10 × 14	3220
3	17 MV	6 × 12	1935
4	17 MV	6 × 12	970
5	12 MeV	6 × 12	1100

TABLE 23-4. Nasopharynx Cancer: Results of Radiation Therapy

Institution and Dates of Treatment	No. Patients	5-Y Survival	Percentage of T4 Lesions	Percentage of Lymphoepithelioma
M. D. Anderson[32] (1954–1977)	251	52% (Actuarial)	30%	45%
University of Florida* (1964–1978)	47	44% (Direct)	53%	24%
Stanford University[23] (1956–1973)	74	59% (Direct)	11%	36%
University of California[33] (1940–1968)	146	37% (Direct)	Not available	25%

* University of Florida data; patients treated October 1964 to April 1978; analysis April 1980 by J. W. Gefter, MD.

sists for 3 to 4 weeks after the completion of treatment. If tumor does not involve the mucosa of the oropharynx, dexamethasone mouth rinse may be used to treat irradiation-induced mucositis. Dryness is always present and may be severe. Loss of taste and appetite often is quite profound, but both return 1 to 6 months after completion of treatment.

The eustachian tube is in the high-dose area, and obstruction may occur, resulting in secondary otitis media and hearing loss. This condition can be corrected by polyethylene tubes inserted through the eardrums to drain the middle ears. The obstruction often improves or clears completely after mucosal healing of the nasopharynx. Politzerization of the eustachian tubes may reopen the canal.

Although mild nausea may occur, severe nausea and vomiting are uncommon. The overall effect of the treatment is wearing on patients, and a period of several months may be required for patients who were successfully irradiated to regain their sense of well-being.

Diagnosis and Management of Recurrence

Almost all recurrences of squamous cell carcinoma are diagnosed within 2 years, but lymphoepithelioma may reappear many years after initial therapy. Headache and cranial nerve palsies usually indicate recurrence. Recurrence in the base of the skull or middle cranial fossa may be difficult to diagnose even with CT or MRI. The single best study to confirm recurrent tumor is MRI. This should be a focused examination with thin sections and high-resolution technique. At minimum, patients should be studied in two planes. The scan should be done before and after the injection of paramagnetic contrast agent. At some point T2-weighted images should be done.

Retreatment with irradiation for recurrence may be rewarding, particularly for the lymphoepitheliomas.[10,31] Patients have been kept free of local disease for various lengths of time by irradiation through a limited portal with a high-energy beam or with brachytherapy sources inserted into the nasopharynx by mold technique.

In recent years, another option that has been available for managing an early local recurrence is resection by an experienced skull base surgeon.[44]

RESULTS OF TREATMENT

The 5-year survival rate has improved considerably over the last 30 years. Survival rates of 10% to 30% were reported before the use of supervoltage techniques. More recent reports give an encouraging 44% to 59% 5-year survival rate (Table 23-4). The gains have not come from earlier diagnosis, but from better imaging of the primary lesion, use of a larger treatment volume and higher doses, and comprehensive irradiation of the neck. Control at the primary site and neck versus stage and histologic type for a series of patients treated at M. D. Anderson Hospital are outlined in Tables 23-5 and 23-6. Stage for stage, control rates are higher for lymphoepithelioma than for squamous cell carcinomas. The 5-year disease-free survival rates by histologic type in the M. D. Anderson Hospital series[32] were as follows: squamous cell carcinomas, 42%; lymphoepithelioma, 65%; and unclassified carcinomas, 14%. The incidence of distant metas-

(text continues on page 624)

TABLE 23-5. Local Control in Patients From M. D. Anderson Hospital

T Stage	Squamous Cell Carcinoma	Lymphoepithelioma	Unclassified Carcinoma	Total
T1	14/15 (93%)	17/17 (100%)	2/2	33/34 (97%)
T2	44/57 (77%)	40/43 (93%)	2/2	86/102 (84%)
T3	8/18 (44%)	24/26 (92%)	1/1	33/45 (73%)
T4	21/35 (60%)	24/27 (89%)	5/8	50/70 (71%)

(Mesic JB, Fletcher GH, Goepfert H. Megavoltage irradiation of epithelial tumors of the nasopharynx. Int J Radiat Oncol Biol Phys 1981;7:452)

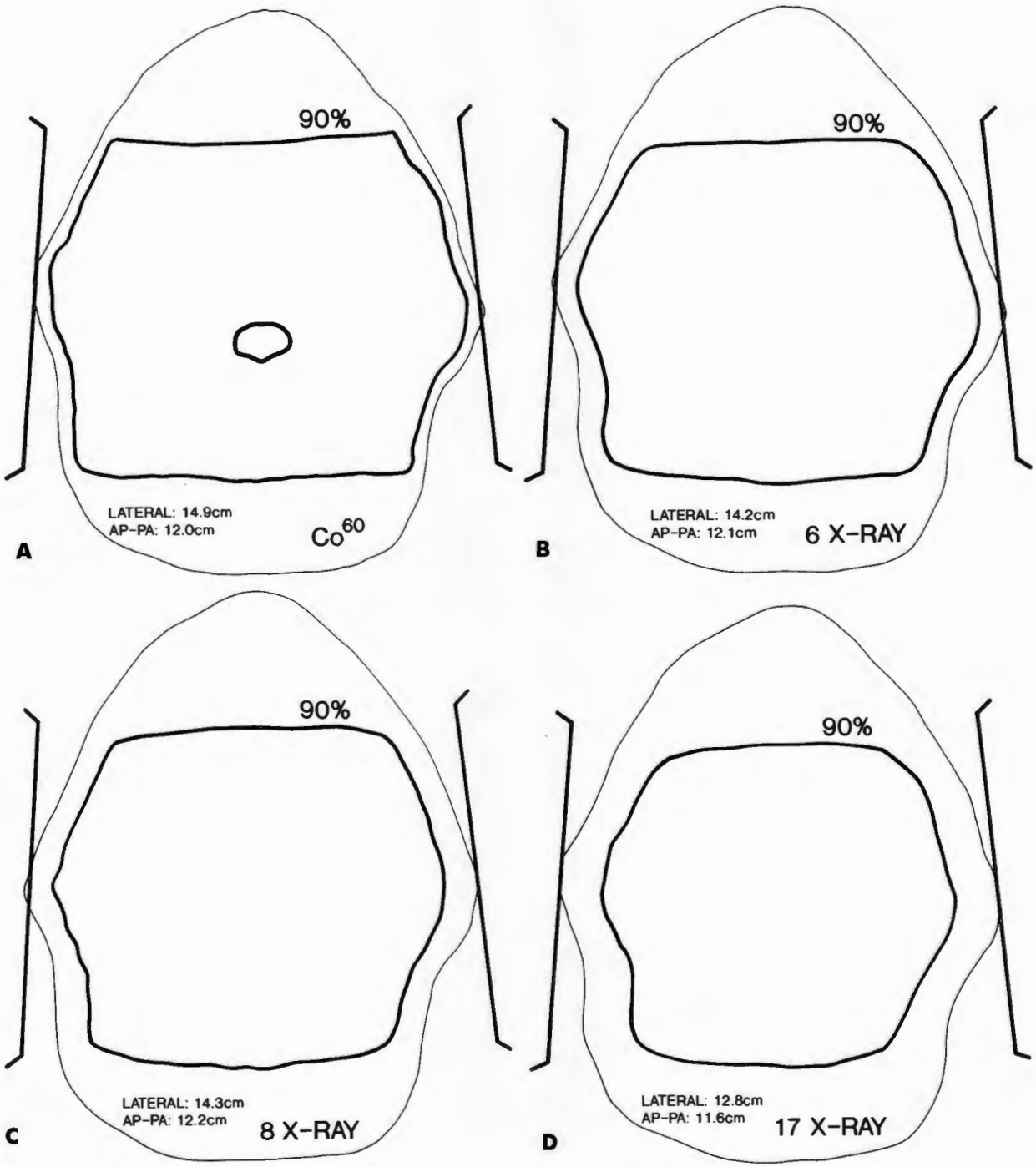

Figure 23-20. Central axis isodose distribution for parallel opposed fields with a 5-degree posterior tilt using various beam energies. (*A* through *D*) Initial fields. (*E* through *H*) Reduced fields. The dimensions for the 90% isodose volume for each contour are indicated. Both the anterior–posterior (AP-PA) and the lateral dimensions of the 90% isodose volume are smaller for a 17-MV x-ray beam, compared with those for lower beam energies.

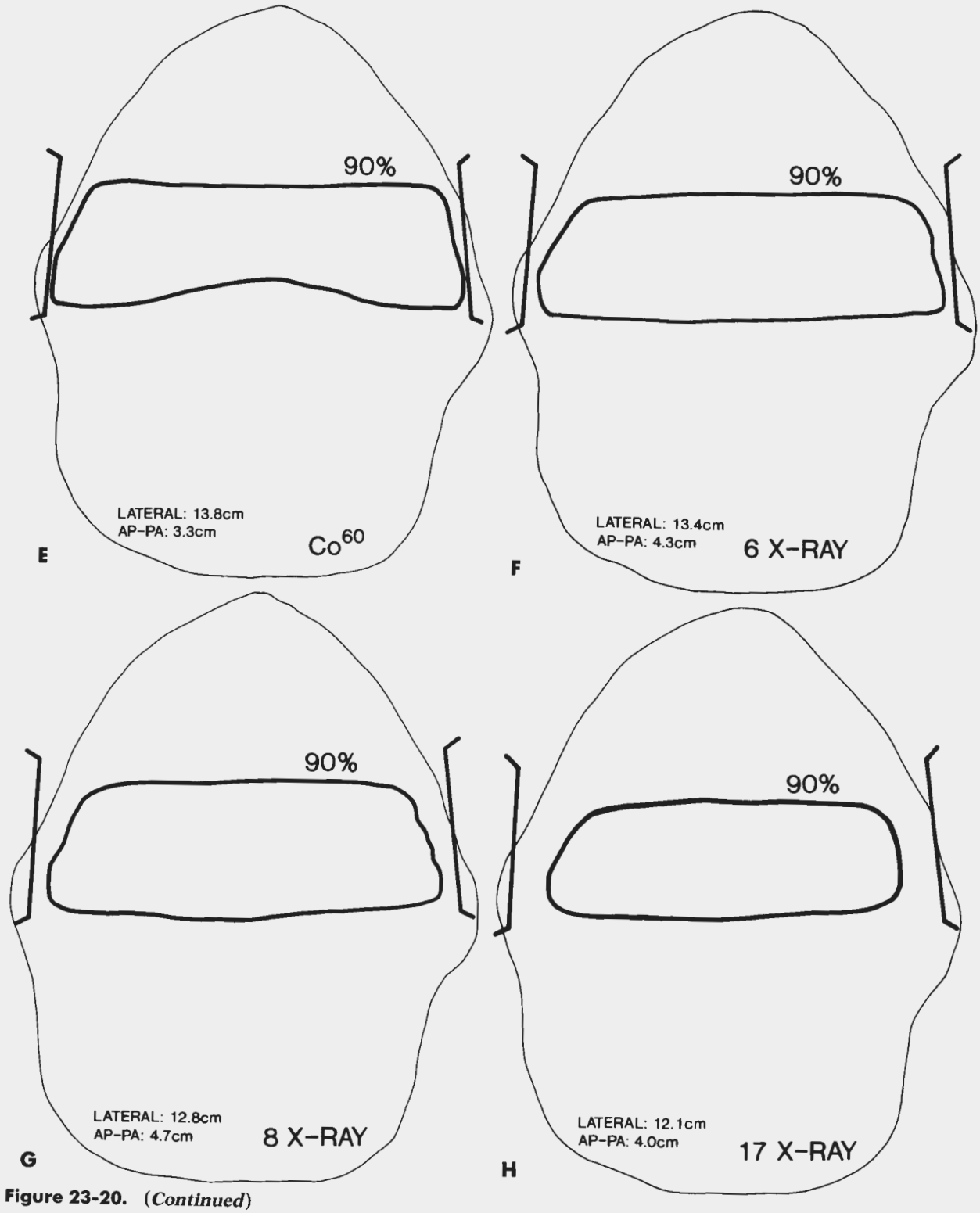

Figure 23-20. (*Continued*)

TABLE 23-6. Control of Disease in the Neck Nodes in Patients From M. D. Anderson Hospital

N Stage	Squamous Cell Carcinoma	Lymphoepithelioma	Total
N0	21/21 (100%)	14/14 (100%)	35/35 (100%)
N1	16/19 (84%)	11/11 (100%)	27/30 (90%)
N2A	10/11 (91%)	14/15 (93%)	24/26 (92%)
N2B	15/18 (83%)	13/15 (87%)	28/33 (85%)
N3A	5/9 (56%)	5/7 (71%)	10/16 (63%)
N3B	35/47 (74%)	48/51 (94%)	83/98 (85%)

(Mesic JB, Fletcher GH, Goepfert H. Megavoltage irradiation of epithelial tumors of the nasopharynx. Int J Radiat Oncol Biol Phys 1981;7:452)

tasis was as follows: squamous cell carcinoma, 23%; lymphoepithelioma, 35%; and unclassified carcinoma, 30%.[32] The cause of death in squamous cell carcinoma is usually local–regional disease, whereas it is generally by distant metastasis in lymphoepithelioma.[32]

Parameters that adversely affect prognosis include the following: extensive primary tumor, cranial nerve involvement, positive neck nodes below the level of the thyroid notch, positive nodes at multiple levels in the neck, WHO type 1 histologic type, ADCC (EBV antibody-dependent cellular cytotoxicity) titer less than 1 : 7, 680 for WHO type 2 and 3 tumors, and age older than 40 years.[20,34–36,49] All other parameters being equal, the prognosis for pediatric patients is not significantly different from adults.[24,37]

Results of Treatment of Recurrence

Fu and coworkers,[19] from University of California at San Francisco, report a 41% 5-year survival rate and a 25% 10-year survival rate for patients with localized recurrence selected for retreatment. The longer the interval to recurrence, the better the prognosis. Fu and associates[19] reported six examples of soft tissue necrosis and three of osteonecrosis of the sphenoid sinus; central nervous system necroses were reported. Yan and colleagues,[46] from Beijing, reported 5-year survival rates of 19% (9 of 48) after irradiation for local recurrence alone, and 11% (5 of 46) after retreatment of recurrent disease in the primary site and neck. Wang[45] reviewed 51 patients retreated with irradiation for local recurrence after radiation therapy at Massachusetts General Hospital (Boston). Thirty-eight patients (32 initially had T1–2 cancers and six had T3–4 lesions) received 6000 cGy; 45% survived 5 years, and 39% survived 10 years.[45] Survival after retreatment was adversely affected by advanced (T3–4) initial T stage and disease-free interval less than 2 years.[45]

Fisch[15] reported resection of locally recurrent nasopharyngeal carcinomas using an infratemporal fossa approach. Surgically induced deficits included an ipsilateral complete conductive hearing loss and sacrifice of the second division on the fifth cranial nerve in T1–2 tumors, and the second and third divisions on the fifth cranial nerve for T4 tumors. Fisch[15] operated on six patients with persistent T1–2 lymphoepithelioma, and all six patients remained alive and disease-free 5 years after resection. Seven patients with locally recurrent T4 squamous cell carcinomas also had resection, and all seven patients died of locally persistent disease within 2 to 3 years of surgery.

FOLLOW-UP POLICY

Documentation of local recurrence is important, but salvage is rarely possible if high-dose, large-volume treatment has been given initially.

The neck should be have careful follow-up because a patient with isolated neck recurrence may be salvaged by neck dissection.

Follow-up includes careful observation and routine laboratory testing for possible endocrine hypofunction of the thyroid and pituitary and laboratory testing for suspicious symptoms. Dental care must be closely monitored because of the severe xerostomia.

Patients with nasopharyngeal cancer have a significantly lower incidence of second primary malignancies compared with patients treated for cancers arising in other head and neck sites.[11] Cooper and associates[11] noted that the risk of second primary cancers was about the same as the incidence of first malignancies in an age-matched and gender-matched control population.

COMPLICATIONS OF TREATMENT

The unavoidable irradiation of part of the brain, including the hypothalamus, temporal lobes, and pituitary, to doses between 6000 and 7000 cGy is associated with a very low risk (less than 1%) of brain necrosis. Primary or secondary hypopituitarism due to a hypothalamic lesion has been reported.[25] Hypothyroidism may result from either the direct irradiation of the thyroid gland or an indirect effect on the pituitary.[41] Delayed bone age and growth failure may be seen in young patients. A transitory central nervous system syndrome may appear 2 to 3 months after irradiation.[7] The greater the volume of central nervous system that is irradiated, the longer it takes patients to recover a sense of well-being; some patients require 6 months to 1 year to regain their general strength. General weakness and extreme fatigue are symptoms of low serum cortisol levels. Radiation myelitis of the cervical cord or brain stem is the most severe central nervous system complication.

Trismus occurs to varying degrees, caused by fibrosis and contracture of the pterygoid muscles, rather than by temporomandibular joint fibrosis. This complication is more likely in patients who are treated with two opposing portals for the entire course. Palsy of any cranial nerves IX through XII, especially the hypoglossal nerve, may occur several years after treatment.

Eye complications such as retrobulbar optic neuritis may develop owing to irradiation of the optic nerve. Irra-

diation of the posterior eyeball to high doses may produce a radiation retinopathy with decreased vision or even total loss of one eye (see Chap. 13).

Mesic and associates[32] reported a 6% incidence of major irradiation complications in a series of 251 patients treated at M. D. Anderson Hospital. The following complications were noted: myelitis, eight (3%); paralysis of any of cranial nerves IX through XII, three (1%); massive neck fibrosis, two (1%); pharyngeal wall necrosis, two (1%); and base of skull necrosis, one (0.4%). The overall treatment-related mortality rate was 7 of 251 (3%).[32] Peters and colleagues,[38] from M. D. Anderson Hospital, observed that adjuvant chemotherapy, especially bleomycin, resulted in a markedly increased incidence of fibrosis, especially in the neck, compared with irradiation alone.

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24

JUVENILE ANGIOFIBROMA

RODNEY R. MILLION, NICHOLAS J. CASSISI, SCOTT P. STRINGER, AND ANTHONY A. MANCUSO

Juvenile angiofibroma (JAF) is an uncommon, histologically benign vascular tumor with the potential to kill or cause serious morbidity due either to uncontrolled growth or to complications of the treatment. The tumor occurs almost exclusively in males; a rare case in a female has been documented in which female sex chromosomes were confirmed. Most tumors appear around the age of 12 to 15, but an occasional diagnosis is made before the age of 10 and after the age of 25. There is a case report of diagnosis at age 62, but the diagnosis after age 25 should be suspect.[18] Spontaneous regression has been reported but does not occur often.

In six tumors studied by Johns and coworkers no estrogen receptors were found.[13] Farag and associates demonstrated androgen-specific receptors in all seven tumors that were analyzed; serum levels of dihydrotestosterone, testosterone, and estradiol-17β were normal. All seven males had normal sexual development.[9]

ANATOMY

The nasopharynx has often been regarded as the site of origin. Neel and coworkers determined the site of origin based on the patterns of spread, the clinical picture of early lesions, and the findings at surgery to be the posterolateral wall of the nose near the sphenopalatine foramen.[17] Sessions and associates noted that irradiated lesions tended to regress toward the sphenopalatine area.[19] These clinical observations have been confirmed by computed tomography (CT) and magnetic resonance imaging (MRI).

PATHOLOGY

Juvenile angiofibroma consists of large, dilated blood vessels with varying amounts of fibrosis, the fibrous stroma increasing in long-standing or recurrent tumors. There is no true capsule present. Because the tumor grows by expansion, there may be nerve, bone, and focal calcification within the tumor, but mucous glands and lymphoid aggregates are not normally present. Histologically, the lesion should be differentiated from nasal polyps, pyogenic granulomas, sclerosing hemangiomas, hemangioendotheliomas, and fibrosarcomas.

PATTERNS OF SPREAD

The early tumors are localized to the posterior nares, nasal cavity, or nasopharynx with or without early extension to a paranasal sinus. There are two case reports of lesions presenting as a cheek mass that, when dissected, involved the pterygopalatine fossa without a nasal component.[19] As the tumor enlarges it tends to extend along the roof of the nose and anteriorly into the nasal cavity, usually confined to the ipsilateral nasal cavity. The hard palate may be eroded, producing a submucosal mass in the palate. Posterior growth occurs into the nasopharynx and often fills the entire nasopharynx, producing an obvious bulge in the soft palate. The tumor typically grows through the sphenopalatine foramen into the pterygopalatine fossa. Tumor commonly extends laterally through the pterygopalatine fossa to the infratemporal fossa, where it grows anteriorly, pushing the posterior wall of the maxillary sinus forward and eventually destroying it by pressure. Less often, the tumor may enter the maxillary sinus through the medial wall of the antrum. The infratemporal fossa may be filled with tumor, which may produce enlargement of the cheek. Large masses extend above the zygoma. Tumor in the pterygopalatine fossa gains access to the orbit through the inferior orbital fissure and can continue to grow intracranially from that point; such intracranial spread is usually just lateral to the cavernous sinus. Superior extension may also occur through the floor of the middle cranial fossa, usually in the vicinity of the ptery-

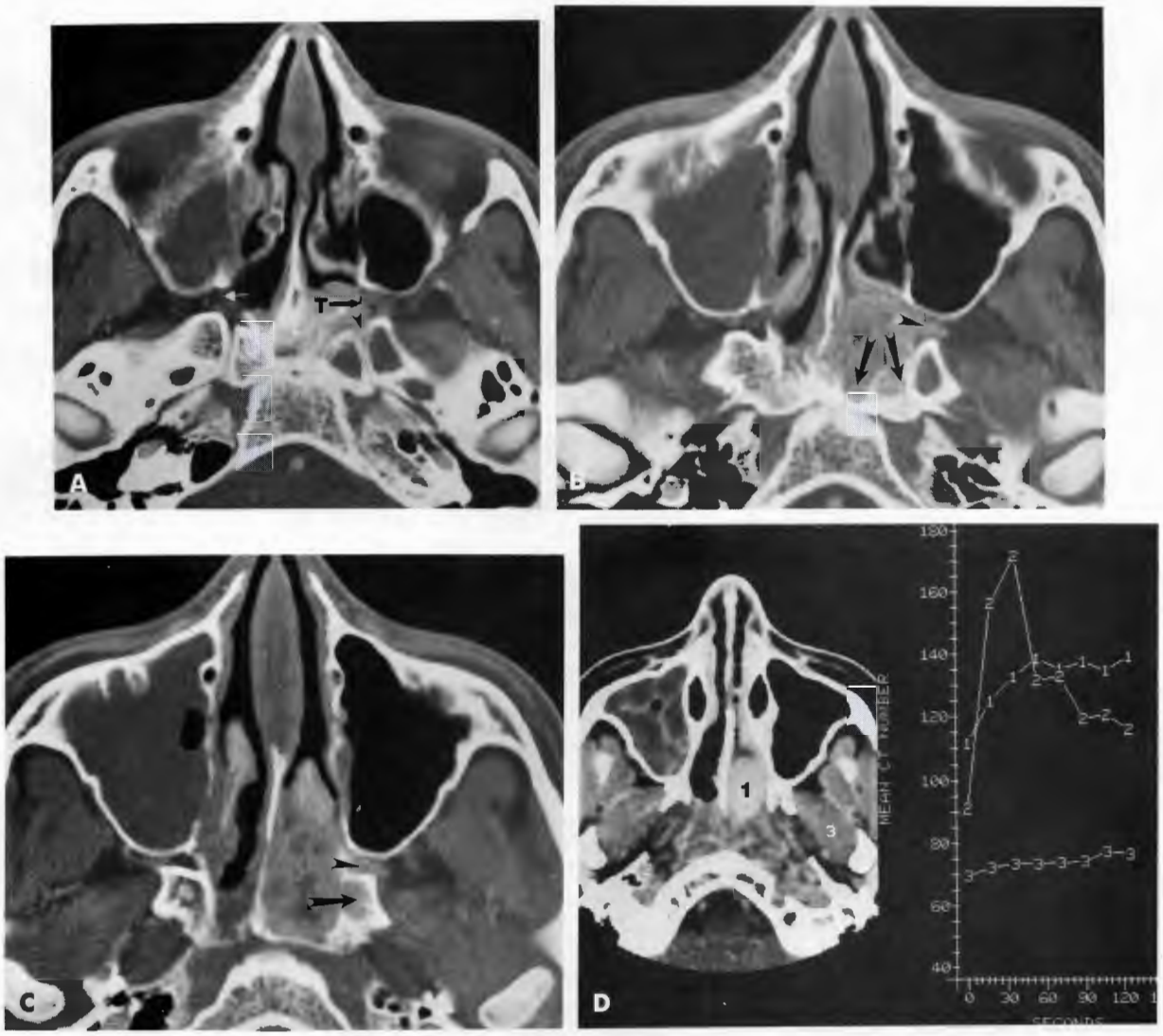

Figure 24-1. A teenaged boy had nosebleeds, and physical examination strongly suggested the presence of a juvenile angiofibroma in the posterior nasal cavity and nasopharynx. (*A*) Axial, contrast-enhanced CT shows the top of the tumor (T) extending into the sphenopalatine foramen (*arrow*); compare with the normal sphenopalatine foramen on the opposite side (*white arrow*). The mass is also beginning to extend into the vidian canal (*arrowhead*). (*B*) A section about 5 mm inferior to that in *A* shows the tumor growing into the basisphenoid and pterygoid process (*arrows*) and extending into the pterygopalatine fossa with early spread through the pterygomaxillary fissure (*arrowhead*). From here the tumor could extend into the infratemporal fossa. (*C*) A section about 3 mm inferior to that in *B* shows the tumor extending into the posterior nasal cavity, pterygoid fossa (*arrow*), and the mid pterygopalatine fossa (*arrowhead*). Note the remodeling of the posterior wall of the antrum in response to the presence of tumor; compare the early changes seen here with the marked "displacement" of the posterior antral wall in more advanced lesions in other figures. In the past, anterior displacement of the posterior wall of the maxillary antrum was considered "pathognomonic" of juvenile angiofibroma; however, this may be seen in any slow-growing lesion in this region. (*D*) A dynamic CT examination was done during injection of the first bolus of contrast material used in the study. Note that the tumor (*curve 1*) rises to a peak slightly more slowly than does the peak seen in the carotid artery (*curve 2*); the tumor later remains at a level of contrast accumulation somewhat higher than that of the artery. This confirms the nearly arterialized flow rate in these lesions and the tendency for contrast material to remain within the interstices of the tumor rather than to wash out rapidly as seen in the carotid. Curve 3 is contrast accumulation in muscle and is used as a control for relatively hypovascular tissue. Dynamic studies such as these are not required in the evaluation of these tumors because they are not specific; this is shown to relate the CT and MRI appearance so that seen on angiography. (*E*) A lateral view from a selective external carotid arteriogram shows the relatively small angiofibroma being supplied almost exclusively by the branches of the distal internal maxillary artery.

Figure 24-1. (*Continued*)

goid process, with eventual intracranial extension into the cavernous sinus. Invasion through the base of skull at this location is usually through growth from the pterygopalatine fossa into the pterygoid (vidian) canal and growth cephalad in the pterygoid fossa. Tumors spreading superiorly from the nasal cavity invade the sphenoid sinus and may, in advanced cases, expand into the sella turcica with displacement of the pituitary gland; pressure on the optic chiasm may result in blindness. Once the tumor has invaded the cranial skull base, it may appropriate blood from the internal carotid artery; its predominant supply is from the internal maxillary and ascending pharyngeal branches of the external carotid artery. One instance of simultaneously occurring double JAFs has been reported.[19] Lymphatic and vascular metastases have not been reported.

CLINICAL PICTURE

The signs and symptoms are not always representative of the size of the lesion. Patients with minimal findings may turn out to have extensive lesions, while small lesions may produce alarming nosebleeds. Nasal obstruction and epistaxis are the most common presenting symptoms. Early cases of nasal obstruction occur on only one side. Patients may present with moderate swelling of the cheek and, less commonly, proptosis. Other symptoms include nasal speech, sneezing, and nasal discharge. Conductive hearing loss occurs secondary to obstruction of the eustachian tubes. Cranial nerve palsies occur (eg, involving the trigeminal nerve) but are uncommon. Superior extension of the tumor may involve the optic nerve and produce partial blindness.

Physical Examination

The characteristic gross appearance of a JAF is a dark red to pale blue, submucosal, smooth, nodular neoplasm, sometimes with evidence of recent hemorrhage. The lesions become more fibrous with time, which explains the variation in color; they are easily confused with a nasal polyp or the "mulberry turbinate."

There may be obstruction of one or both nasal cavities with an obvious mass. The tumor may be seen extending through the posterior nares into the nasopharynx, completely filling the nasopharynx, and may cause bulging of the soft palate forward. There may be a submucosal bulge into the hard palate and gingivobuccal sulcus. Proptosis and an obvious, diffuse, soft swelling over the maxillary antral area and cheek may be evident. A larger, more extensive tumor may occasionally extend into the upper neck or temporal fossa. Cranial nerve palsies may occur in patients with lesions invading the skull base, orbital apex, and cavernous sinus. Sexual maturation may be retarded or absent.

METHODS OF DIAGNOSIS AND STAGING

The diagnosis of JAF is usually established by a combination of clinical factors, typical growth pattern and morphology on contrast-enhanced CT or MRI, and arteriography. Biopsy may produce serious hemorrhage. If only a small sample is removed from the periphery of a JAF, it may not be representative and a mistaken diagnosis may occur.[20] A characteristic JAF on imaging studies is considered equivalent to a biopsy if the patient has a typical clinical picture. We only insist on biopsy before radiation therapy or surgery if the clinical and imaging data are equivocal (Fig. 24-1).

Diagnostic Imaging

Contrast-enhanced CT and contrast-enhanced MRI are the mainstays of diagnosis in patients suspected of having a JAF. Arteriography plays an important role in both diagnosis and management. Magnetic resonance angiography, at its current stage of development, adds no additional diagnostic information.

Imaging of the Normal Anatomy

The anatomy related to the diagnosis and management of JAF is shown in Figures 23-12 and 23-13 in Chapter 23.

Technique of Examination

The CT and MRI techniques for a suspected JAF are the same as those for the nasopharynx (see Chap. 23). The standard MRI study should emphasize multiplanar T1-weighted images with contrast enhancement. T2-weighted images are done to differentiate obstructed sinuses from those invaded by tumor and to look for evidence of brain invasion. CT should be done in the axial and coronal planes with contrast material given by one of the techniques outlined in Chapter 4. Precontrast CT is not necessary. Noncontrast CT may be used as a complement to MRI for evaluating bone detail.

Diagnostic arteriography is relatively simple and requires only an injection into the common carotid artery and good quality subtracted views. When more careful angiographic mapping of the lesion is required, selective internal and external carotid injection will help determine the amount of intracranial supply (usually from branches of the cavernous segment of the carotid artery). Selective external carotid injection will serve as a road

map for preoperative embolization and uncover any potentially dangerous anatomic variants or anastomoses (eg, origin of the ophthalmic artery from the middle meningeal). The contralateral carotid system should be studied if embolization and surgery are contemplated. The vertebrobasilar system is not routinely evaluated.

Embolization is accomplished with subselective catheterization of the external carotid artery. In the past, this was always done within 24 hours of surgery because the embolic material usually lodged in larger vessels, leaving the vascular matrix of the tumor still patent, and was therefore a stimulus for the rapid establishment of collateral circulation. Newer endovascular techniques and materials allow for the obliteration of the tumor bed as well as larger feeding vessels, and some delay between the procedure and surgery is allowable. The nuances of embolization vary with the interventional radiologist and are in a steady state of improvement.

Indications for Study

The indications for imaging and arteriography may be separated into several basic categories.

DIAGNOSIS. The clinical situation usually makes the presumptive diagnosis of JAF likely. CT or MRI may be used initially. MRI is preferred because it can show the typical spread pattern of a JAF and its internal morphology as well as its intense enhancement with intravenous contrast medium (Fig. 24-2).[16a] The branching flow voids and visualization of a vascular pedicle on MRI make the diagnosis nearly certain. With CT, the enhancement and spread pattern will be obvious, but the hypervascularity will only be suggested indirectly by enlargement of the internal maxillary and ascending pharyngeal arteries and their branches. Atypical features strongly suggest the diagnosis is not JAF and can direct the patient to biopsy rather than arteriography for definite diagnosis. Arteriography can be done in lieu of biopsy for confirmation of the diagnosis as long as all other clinical and imaging findings are characteristic of JAF.

DETERMINATION OF EXTENT OF LESION. The extent of a JAF is the most important factor in selecting therapy. MRI, CT, and angiography help to establish whether there is any gross intracranial extension or abnormal vascular supply (Figs. 24-1 through 24-3). CT and MRI also map the tumor's extent in other directions, thereby helping with planning a specific surgical approach. Both CT and MRI can show whether sinuses are obstructed or invaded by tumor (see Chaps. 4, 22, and 23). CT demonstrates bone detail better. This can be especially important in lesions invading the base of the pterygoid process; this is a common site of incomplete excision (Fig. 24-4).

FOLLOW-UP. CT or MRI may be used in follow-up of patients after therapy. MRI is usually chosen at our institution because contrast medium is usually not required and multiplanar sections are easier to obtain. Residual, stable abnormalities have been seen from 6 months to as long as 12 years after radiation therapy (Fig. 24-5). Biopsy has not been performed of these abnormalities, and their nature is conjectural at this point. A residual mass after surgery will usually lead to renewed growth and symptoms.

Differential Diagnosis

Differential diagnosis in this age group includes nasal polyps, nasal cavity and nasopharyngeal carcinomas, esthesioneuroblastomas, lymphomas, sarcomas (including rhabdomyosarcomas, hemangioendotheliomas), benign vascular tumors and malformations (Fig. 24-6), large adenoids, parapharyngeal tumors, foreign bodies, parotid gland tumors, and other rare tumors such as chordomas, meningiomas, and plasmacytomas. A hemangiopericytoma-like intranasal tumor may occur rarely in this age-group.

TREATMENT

Although JAF is a histologically benign tumor, death may occur if the lesion is not treated. Although spontaneous remission has been documented,[11] a policy of observation without treatment is seldom recommended when the tumor is first diagnosed. Serious morbidity or rarely death may occur from the biopsy, arteriography, or operation; reasonable judgment is required in the selection of treatment, since both surgery and radiation therapy are curative.

If the lesion is extracranial and resectable with little danger to the patient, then this is the treatment of choice. For extensive extracranial lesions in which resection will be incomplete or morbid (see Fig. 24-4), and for all lesions with intracranial extension (see Figs. 24-2 and 24-5), radiation therapy is the preferred treatment.

Cummings compared the lifelong risk factors of surgery and radiation therapy and concluded that they are comparable, but the surgical risks are immediate and the radiation risks are delayed (Table 24-1).[5] The doses specified for JAF, 3000 to 3500 cGy over 4 to 5 weeks with supervoltage beams, produce minimal acute and chronic tissue changes even with years of follow-up.

There is considerable long-term follow-up experience in young patients treated with similar doses for lymphoma. The risk of a lethal radiation-induced neoplasm for a single course of supervoltage therapy is estimated to be 1 in 150 for someone 10 to 20 years of age and 1 in 400 for those older than 20 years of age.

The mortality risks associated with surgery include those of general anesthesia, blood transfusion, and the surgical procedure itself. The surgical risk varies, of course, with the extent of tumor to be resected, previous treatment of the tumor, and the experience of the surgical team.

The risk for radiation-induced malignancy associated with radiation therapy in young persons is real and should not be ignored, but it is irrational to recommend surgery and the possibility of immediate death or serious morbidity because of the remote risk of a radiation-induced tumor that has a latent period of at least 7 years and usually more than 20 to 30 years.

Makek and colleagues reviewed the literature in 1989 and found six cases of malignant transformation to sarcoma. Five patients had a history of radiation therapy (multiple courses with total doses greater than 8500 cGy in four cases), and one patient had not received radiation therapy. One of the six sarcomas was cured by operation. Three of the patients had been in their mid-40s at the time of diagnosis, making the original diagnosis of JAF suspect.[16] Cummings also reported a patient who had undergone irradiation and later developed skin cancers.[5]

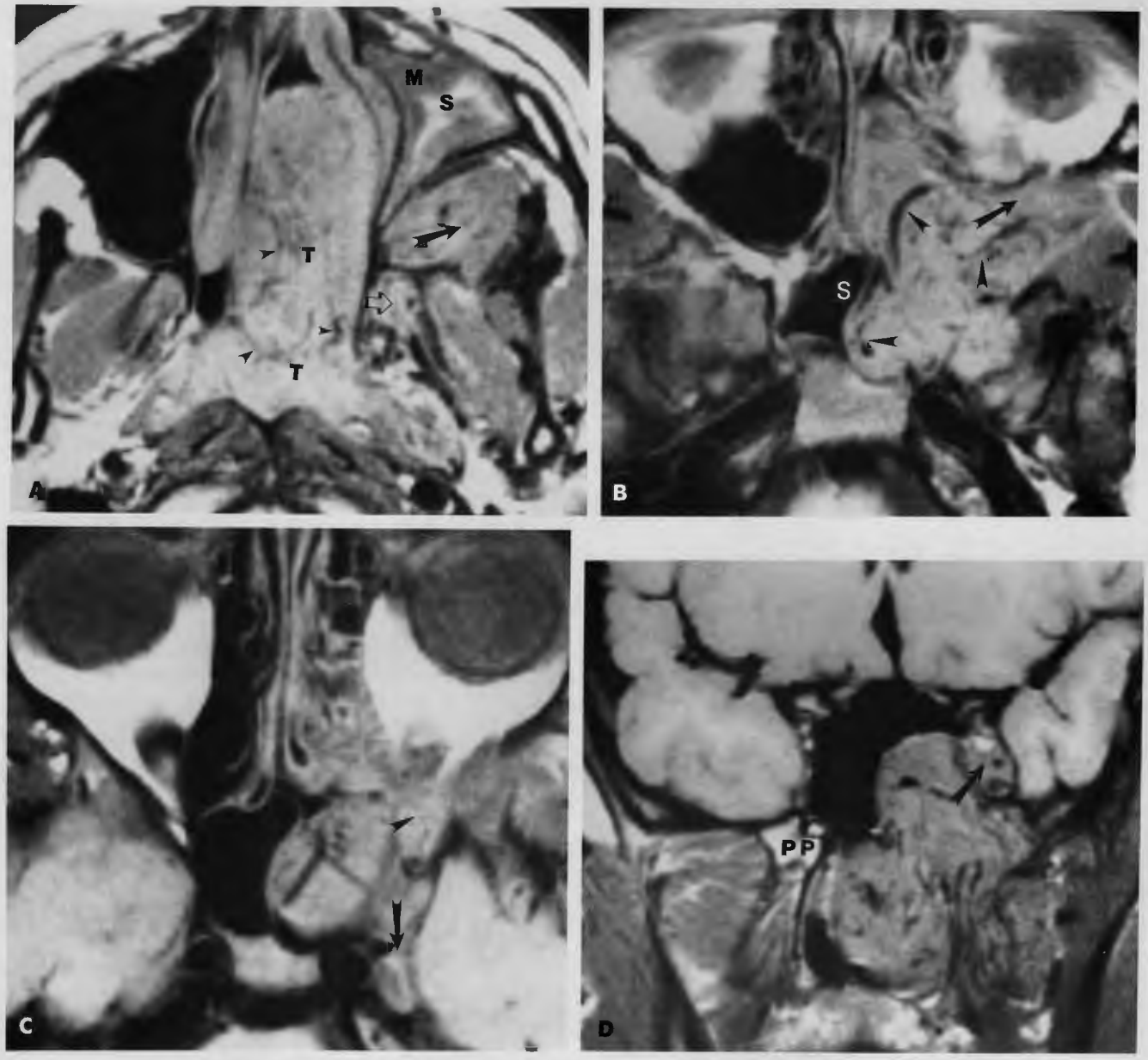

Figure 24-2. A teenaged boy had nasal stuffiness and nosebleeds. (*A*) Axial T1-weighted MRI through the mid nasal cavity and nasopharynx shows a tumor (T) filling the nasal cavity and nasopharynx. The serpiginous structures throughout the mass are large vessels (*arrowheads*). Tumor extends into the infratemporal fossa (*arrow*) and pterygoid fossa (*open arrow*). Even on this T1-weighted image, it is simple to differentiate the tumor in the nasal cavity from the mucosal thickening (M) and secretions (S) in the obstructed maxillary sinus. (*B*) The large vessels within the tumor are even more obvious at this level than in *A* (*arrowheads*). Here the tumor extends into the sphenoid sinus (S), the basisphenoid, and the inferior orbital fissure (*arrow*). (*C*) A T1-weighted axial section, taken about 5 mm cephalad to that in *B* shows continued extension into the inferior orbital fissure (*arrowhead*) and spread posteriorly to the cavernous sinus (*arrowhead*). (*D*) Coronal section confirms the extent of lesion as shown in *A* through *C*. The tumor extends into the cavernous sinus (*arrow*), to the skull base in the region of the pterygoid process (compare with normal pterygoid process [PP] on the other side), laterally into the infratemporal fossa, and medially into the nasopharynx. (Mancuso AA, Hanafee WN. Computed tomography and magnetic resonance imaging of the head and neck, ed 2. Baltimore, Williams & Wilkins, 1985:491–493)

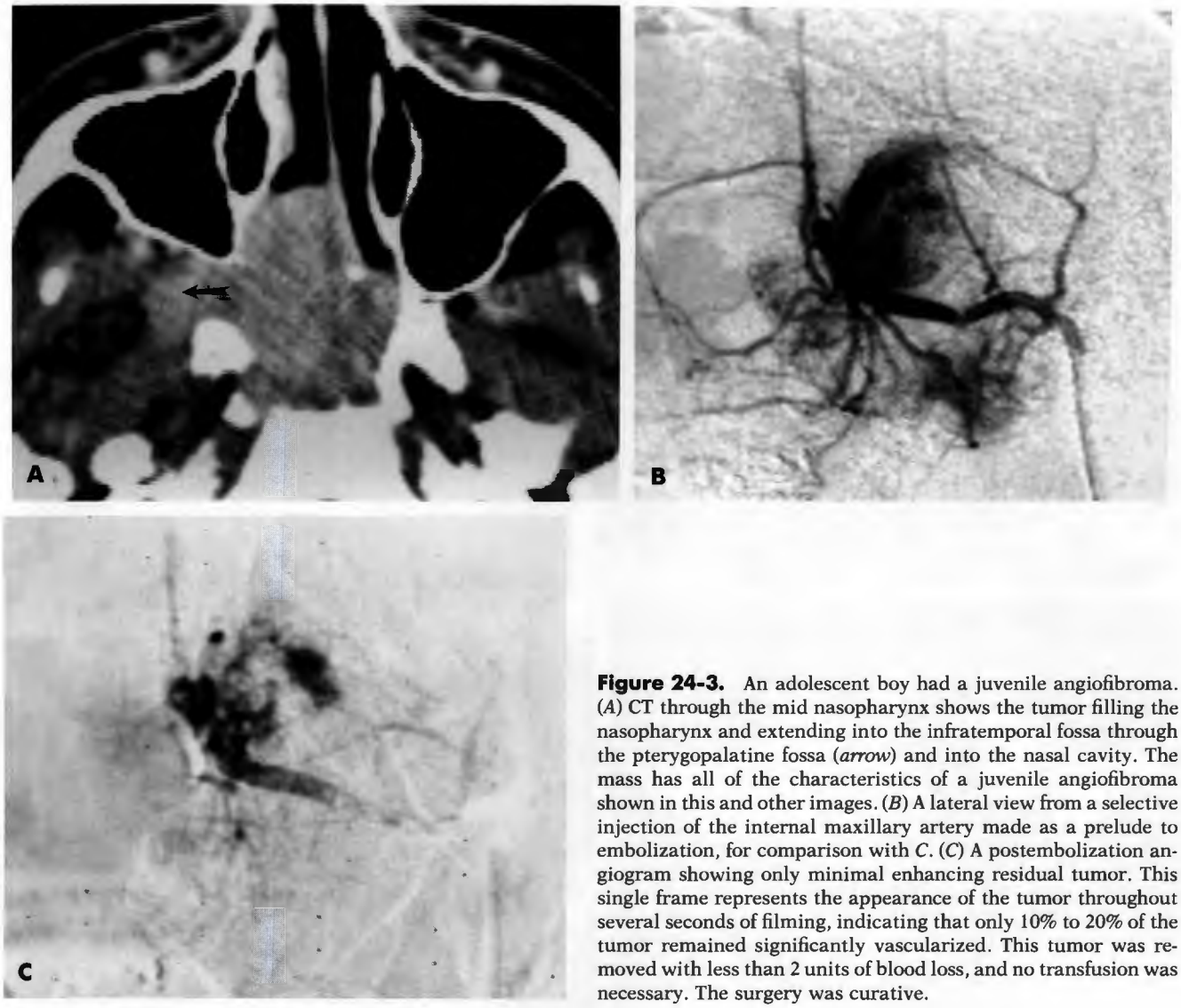

Figure 24-3. An adolescent boy had a juvenile angiofibroma. (*A*) CT through the mid nasopharynx shows the tumor filling the nasopharynx and extending into the infratemporal fossa through the pterygopalatine fossa (*arrow*) and into the nasal cavity. The mass has all of the characteristics of a juvenile angiofibroma shown in this and other images. (*B*) A lateral view from a selective injection of the internal maxillary artery made as a prelude to embolization, for comparison with *C*. (*C*) A postembolization angiogram showing only minimal enhancing residual tumor. This single frame represents the appearance of the tumor throughout several seconds of filming, indicating that only 10% to 20% of the tumor remained significantly vascularized. This tumor was removed with less than 2 units of blood loss, and no transfusion was necessary. The surgery was curative.

TABLE 24-1. Estimated Risk for Fatal Complication Associated With Therapy for Juvenile Angiofibroma

Risks of Operation		Risks of Radiation Therapy	
General anesthesia	1 : 300	Radiation-induced cancer of the thyroid	1 : 400 to 1 : 1200
Arteriagraphy	1 : 1700		
Blood transfusion		Bone/soft tissue sarcoma	1 : 300
Hemolytic treatment	1 : 3500	Arteriography	1 : 1700
Anti-IgA anaphylaxis	1 : 1000	Benign neoplasm	1 : 3500
Hepatitis	1 : 200	Late radiation therapy complications	1 : 1000
Operation	1 : 500	Total estimated death risk (age 15):	Risk unknown
Total estimated death risk	1 : 100	Without blood transfusion	See text
		With blood transfusion	1 : 350
			1 : 100

Note: The exact estimated risks for operation in any single patient will vary with the extent of the neoplasm and whether there has been prior operation or radiation therapy. The risk data for radiation-induced neoplasia are not well established because few patients have been treated to 3000 to 3500 cGy with supervoltage radiation to the head and neck area and then had follow-up for more than 20 years. There is no doubt, however, that the radiation-induced neoplasms have a long latent period, at least 7 years and more often greater than 20 years.

(Data from Cummings BJ. Relative risk factors in the treatment of juvenile nasopharyngeal angiofibroma. Head Neck Surg 1980;3:21–26)

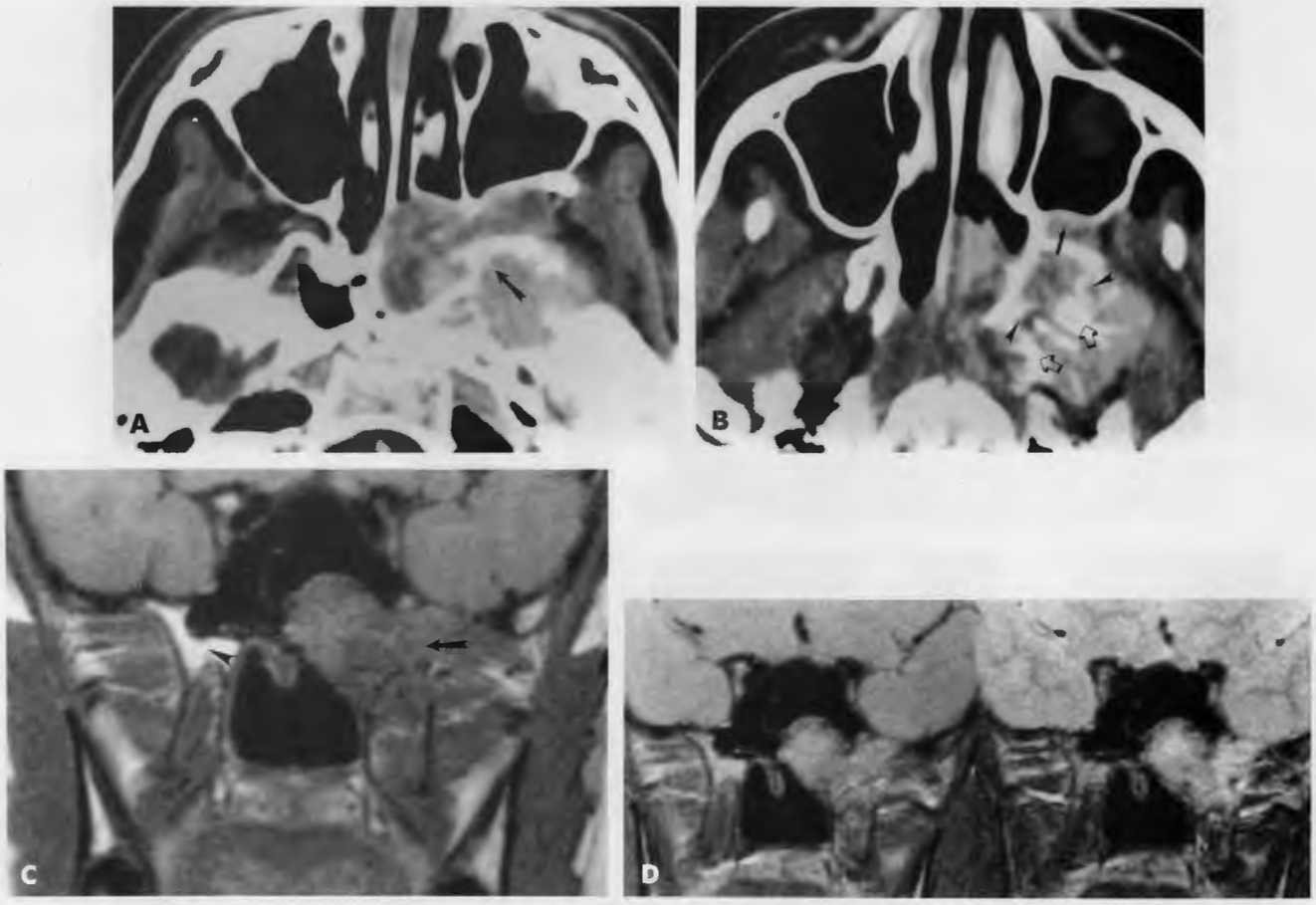

Figure 24-4. An adolescent boy had recurrent juvenile angiofibroma after two previous attempts at surgical cure. (*A*) Axial CT shows the persistent tumor centered in the basisphenoid where it is joined by the pterygoid process (*arrow*). Additional tumor in the sphenoid sinus and pterygopalatine fossa is present. (*B*) A CT section taken about 5 mm below that in *A* shows the predominant spread pattern between the pterygoid plates (*arrowheads*) and a small component of the lesion in the pterygopalatine fossa (*arrow*). Embolic material (*open arrows*) is trapped in the lesion. Angiogram in this patient showed considerable dural blood supply from branches of the internal carotid artery. The patient's parents elected to have radiation therapy rather than surgery when presented with their son's options for retreatment. (*C*) Coronal T1-weighted MRI taken 2 years after radiotherapy. The stable residual tumor is once again centered in the skull base at the junction of the pterygoid process and basisphenoid (*arrow*); compare with the normal skull base in this region on the opposite side (*arrowhead*). (*D*) A spin density and T2-weighted sequence from the same date as the MRI seen in *C*. Despite the prior operations and irradiation, the tumor remains hyperintense to surrounding muscle. *Comment:* Recurrence of juvenile angiofibroma in the upper portion of the pterygoid fossa and at the junction of the pterygoid process and basisphenoid is not unusual. This is believed to be due in part to the rich vascular plexus in this location and the difficulty in getting an adequate margin without doing a formal resection of the skull base. This case also illustrates that radiotherapy does not always result in complete shrinkage of the tumor, even though it is controlled and essentially cured. Stabilization after 25% to 75% reduction in volume of the tumor occurs in at least half of the patients. In some patients, these tumors will disappear completely in response to radiotherapy.

It has been suggested that partial removal of the tumor will reduce radiation portals and ensure a better result. The entire potential area of recurrence would be irradiated, however, so this would not modify the radiation therapy portals. Whenever possible, a single treatment, either surgery or radiation therapy, should be chosen to minimize the total risk.

Surgical Treatment

Arteriography with embolization is carried out before surgery to help minimize blood loss. The timing of the embolization relative to surgery depends on the material used. Several authors have used estrogen before operation and report tumor regression and reduced blood loss.

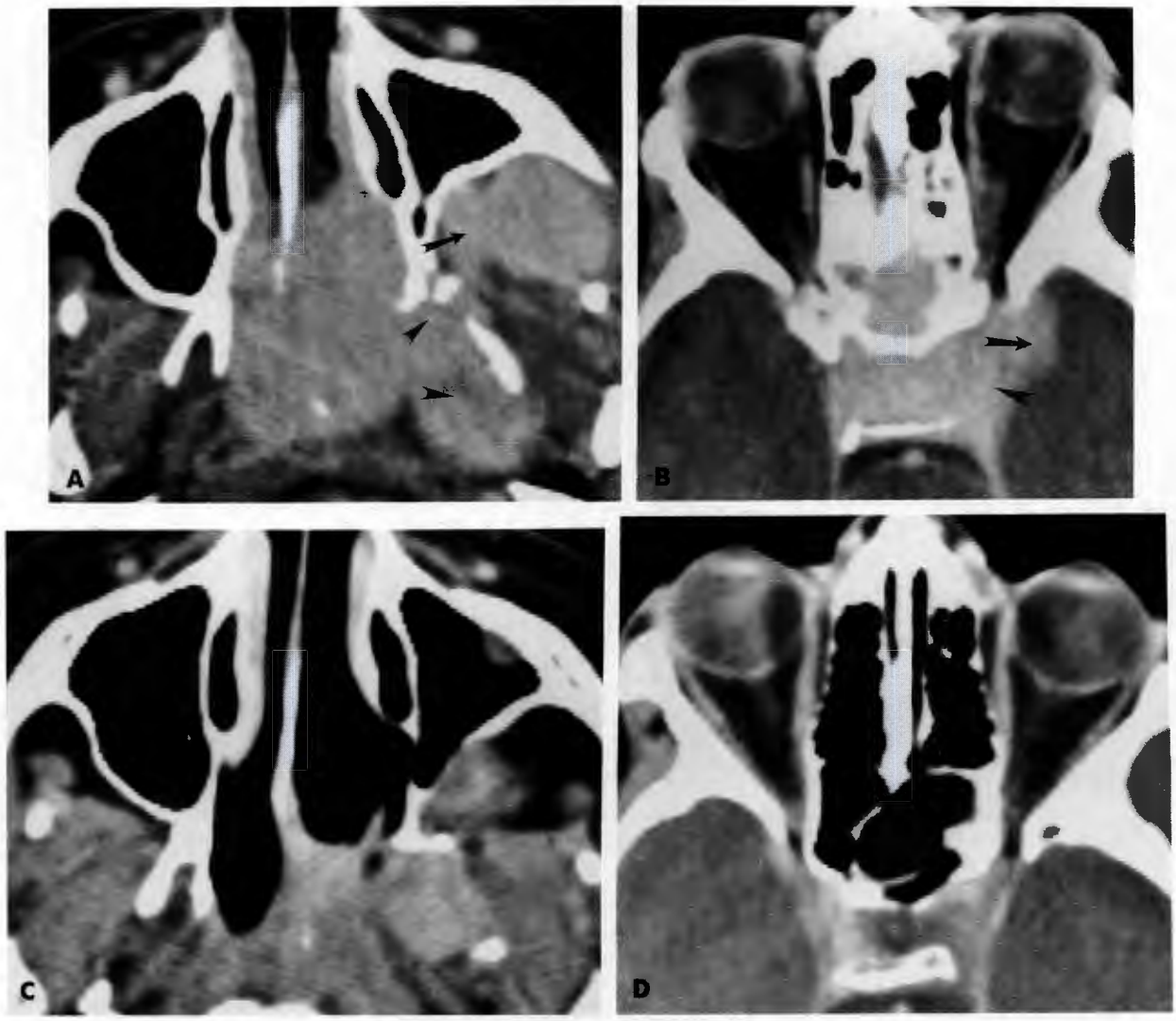

Figure 24-5. An adolescent boy had an extensive juvenile angiofibroma. Angiography showed considerable blood supply from the internal carotid artery. Presented with the options of radiotherapy and surgery, the patient's parents chose radiotherapy. (*A*) Axial, contrast-enhanced CT shows tumor filling the nasopharynx and spreading to the infratemporal fossa (*arrow*) and lateral wall of the nasopharynx and pterygoid fossa (*arrowheads*). (*B*) A section through the upper cavernous sinus shows tumor involving the cavernous sinus (*arrowhead*) and extending into the middle cranial fossa (*arrow*). (*C* and *D*) Posttreatment images correlating with *A* and *B* showing virtually complete regression of the intracranial component of the tumor and very small amounts of residual tumor at other sites. *Comment*: Complete disappearance of a lesion as extensive as this one following radiotherapy would be less usual than a persistent residual mass about 25% of the size of the original tumor. Long-term follow-up in this patient revealed stable residual and no recurrence of symptoms. The patient is now in his mid-20s.

The surgical approach is determined by the size and extent of the tumor. Adequate exposure is essential to prevent hemorrhage and to allow complete resection. Careful blunt dissection is used to tease the tumor off of surrounding normal tissue.

Early Lesions

Tumors limited to the posterior nasal cavity and nasopharynx with minimal extension through the pterygopalatine foramen are approached through a transpalatal incision (see Figs. 24-1 and 24-3). These lesions are usually adherent to the anterior portion of the nasopharynx and the posterolateral wall of the nose. The extensions are teased from their adherent areas and removed through the nasopharynx. If there is significant extension anteriorly and superiorly into the nasal cavity, a lateral rhinotomy may be combined with a transpalatal approach. The midface degloving technique produces better cosmetic results but may not provide as much exposure as the lateral rhinotomy. Minimal extension through the pterygopalatine foramen may be removed, particularly in a previously untreated patient.

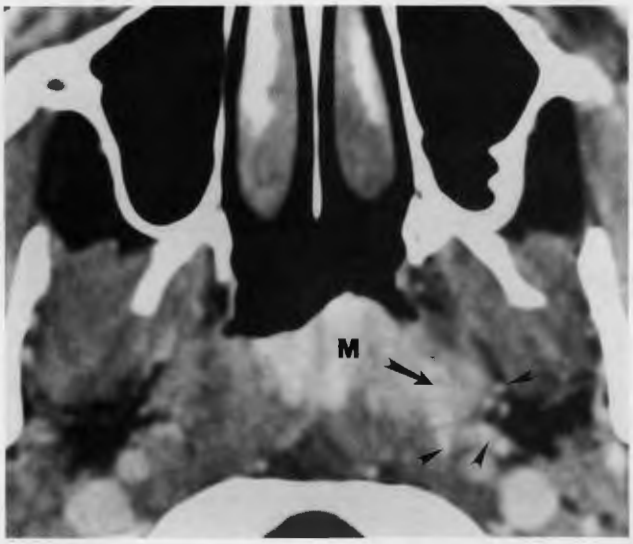

Figure 24-6. An adolescent boy had nosebleeds. Even though the clinical examination of the nasopharynx revealed a mass somewhat atypical in appearance and position for juvenile angiofibroma, this was the favored working diagnosis. CT through the mid nasopharynx showed a mass basically extending along the mucosal surface of the posterior wall of the nasopharynx (M) and into the fossa of Rosenmüller (*arrow*). The distal branches of the ascending pharyngeal artery and accompanying veins were enlarged (*arrowheads*). This mass basically conformed to the distribution of the adenoid tissue within the nasopharynx, and there was no extension into the sphenopalatine foramen or pterygopalatine fossa. *Comment*: This study was interpreted at our institution as *extremely atypical* for juvenile angiofibroma and probably showing some other vascular neoplasm or malformation of the nasopharyngeal wall. The patient had an angiogram done at another institution, and despite the atypical spread pattern this was thought to represent a juvenile angiofibroma. The patient was operated on at that institution without preoperative embolization, and a subtotal resection of the mass resulted because of extensive intraoperative bleeding. Pathologic review of the resected tissue revealed an arteriovenous malformation of the nasopharynx. The patient is currently asymptomatic with no further treatment, although an obvious residual mass is present. Therapeutic embolization would be a preferred method of treatment if the nosebleeds recurred.

Lesions With Major Lateral Extension

Large tumors or recurrent tumors that extend laterally toward the infratemporal fossa require additional exposure for adequate resection (see Fig. 24-4). An extended transantral approach removing the anterior, lateral, and posterior maxillary sinus walls offers excellent access to the pterygopalatine fossa and allows direct ligation of the internal maxillary artery. The majority of laterally extending angiofibromas may be managed with this approach. If further exposure is required, a transmandibular approach combined with a lateral oral pharyngotomy provides exposure of the infratemporal fossa, the parapharyngeal space, and the lateral skull base. Finally, an infratemporal fossa exposure obtained through a retroauricular approach with sacrifice of the middle ear structures may be used in the case of massive infratemporal involvement.

Lesions With Intracranial Extension

Although there are reports of successful removal of intracranial extension, the risks are substantial and radiation therapy should be the initial treatment.[15,21] (See Figs. 24-2 and 24-5.) Should operation be required, a combined extracranial–intracranial approach by an experienced neurosurgeon and head and neck surgeon is advised.

Radiation Therapy

The dose required for a high rate of local control is 3000 to 3500 cGy over 4 to 5 weeks. Each plan is individualized, but most patients are treated with lateral and anterior wedge portals or lateral opposed portals. Most of the reported failures are due to inadequate treatment volume rather than inadequate dosage, and one should err on the side of too large a volume, since the risks (except to the eye) are not changed. Since radiation therapy is generally reserved for patients with large or recurrent lesions, the treatment volume is generous. It is unwise to rely entirely on angiographic findings because all of the supplying vessels may not be perfused. The contrast-enhanced CT scan, MRI, angiography, and the physical examination combine to outline the extent of tumor. The treatment plan and response for a large lesion are shown in Figure 24-7. The initial clinical response to radiation therapy varies from 25% to 100%. Most patients show 30% to 50% evidence of regression on clinical examinations during the course of radiation therapy, but complete regression usually does not occur until months later. About 50% had visible tumor in the nasopharynx or nasal cavity at 1 year in the series reported by Cummings.[5] Complete involution may take over 3 years. Cummings reported a 50% risk of symptomatic regrowth in patients with a visible mass at 2 years. A persistent resolving lesion may be seen on follow-up CT or MRI for several months.

Seven asymptomatic irradiated patients have been evaluated by CT or MRI at varying intervals from 6 months to 14 years. Two patients showed no abnormality at 6 to 10 months. Five showed a residual abnormality with varying degrees of regression for as long as 14 years after irradiation (see Figs. 24-4 and 24-5). The persistent abnormalities have not been subjected to biopsy. Late regrowth is reported but is rare.[14]

Chemotherapy

Goepfert and coworkers reported five cases of recurrent JAF that responded to chemotherapy after conventional local therapy or estrogens had failed. The first-line drugs were doxorubicin and dacarbazine. The second-line regimen was cyclophosphamide, vincristine, and dactinomycin.[10]

Management of Recurrence

Recurrence of JAF after a course of radiation therapy may be treated by surgical removal or with repeat irradiation if the initial doses were 3000 to 3500 cGy. Briant and coworkers reported successful management of 10 surgical failures by radiation therapy.[3] They reviewed

(text continues on page 639)

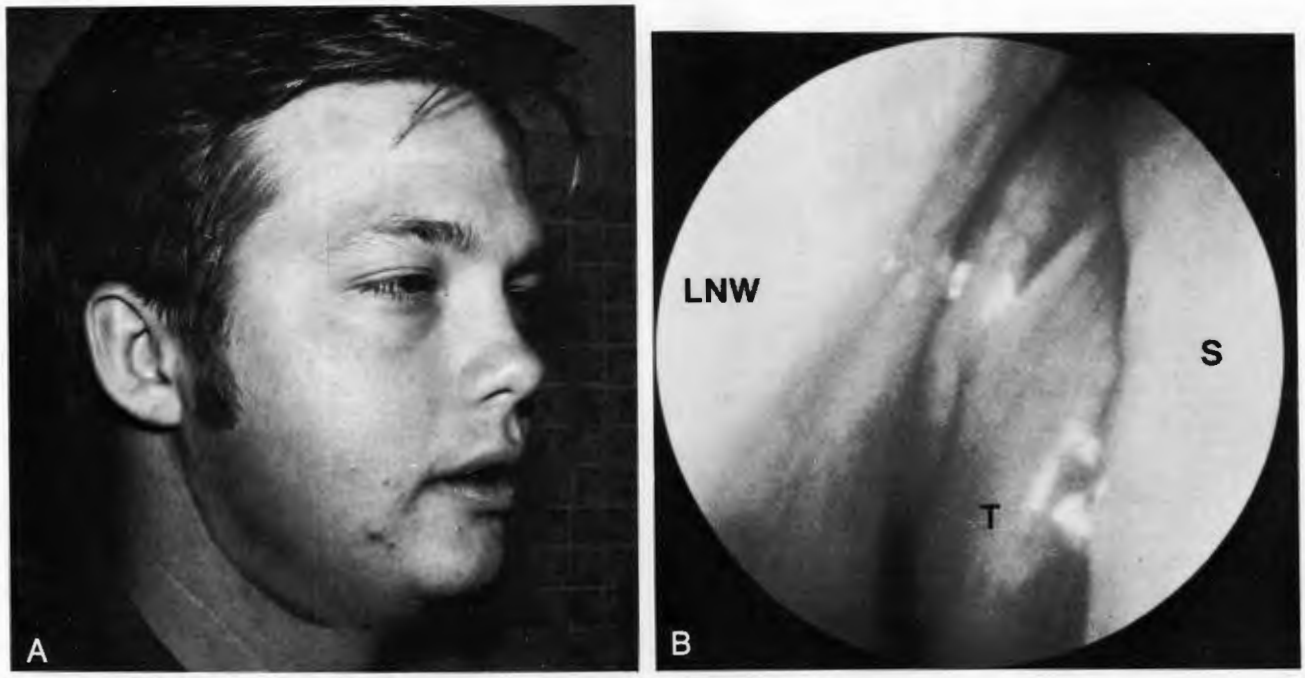

Figure 24-7. A 19-year-old man had a 3-year history of fullness of the right cheek. Exploration of the right parotid revealed a "lipoma." Four months later he developed nosebleeds and right nasal obstruction. (*A*) Diffuse enlargement of the right cheek. There was 3- to 4-mm exophthalmos on the right. (*B*) Tumor mass at 5 cm in right nasal cavity. S, septum; T, tumor; LNW, lateral nasal wall. (Photograph was taken through a fiberoptic nasoscope.) (*C*) Submucosal bulge of right hard palate. There was also fullness in the right gingivobuccal sulcus (not shown). (*D*) Adenoids or tumor in the midline roof of the nasopharynx. Tumor could be seen filling the right posterior choana (not well seen). The left posterior choana is open. (*E*) CT with contrast enhancement. The mass fills the entire infratemporal fossa, extends posteriorly to the styloid process, and produces widening of the pterygopalatine fossa (*arrow*). The mass surrounds but does not destroy the pterygoid plates (*arrowheads*). There is characteristic anterior displacement of the posterior wall of the right maxillary antrum and mass in the right posterior nares. The scan was performed without intravenous contrast enhancement. Postinfusion scans reveal a densely staining mass that, coupled with the characteristic growth pattern, is highly diagnostic for juvenile angiofibroma. (*F*) CT through orbits. There is early extension (*arrow*) through the inferior orbital fissure to the posterior orbit. There was 4 to 5 mm of proptosis on clinical examination. (*G*) Internal carotid angiogram. The anterior portion of the large angiofibroma is clearly demonstrated as a hypervascular mass with blood supply from the internal carotid system. The entire angiofibroma is not outlined. (*H*) Subtracted external carotid artery angiogram. A hypervascular mass (*arrow*) consistent with a large juvenile angiofibroma is well demonstrated. *Treatment plan*: Radiation therapy was recommended because of the extension of the tumor to the orbit and the numerous feeding vessels. (*I*) Simulation film of lateral radiation therapy portal. Wire outlines palpable disease in the right cheek. The thick black line outlines the portal. Note the generous portal size. (*J*) Simulation film of anterior radiation therapy portal. It was not possible to shield the eyeball owing to tumor invasion of the orbit. Patient received 3500 cGy over 4½ weeks, 8-MV x-ray. (*K*) Appearance at 14 months. There was minimal regression at completion of therapy, 75% regression at 6 weeks, and complete clinical regression at 6 months. (*L*) Nasopharynx at 14 months. The submucosal nodule in the roof of the nasopharynx and the tumor in the right posterior nares have disappeared. S, nasal septum; LPN, left posterior nares. (*M*) Appearance of hard palate at 14 months. There was no clinical evidence of disease at 10 years.

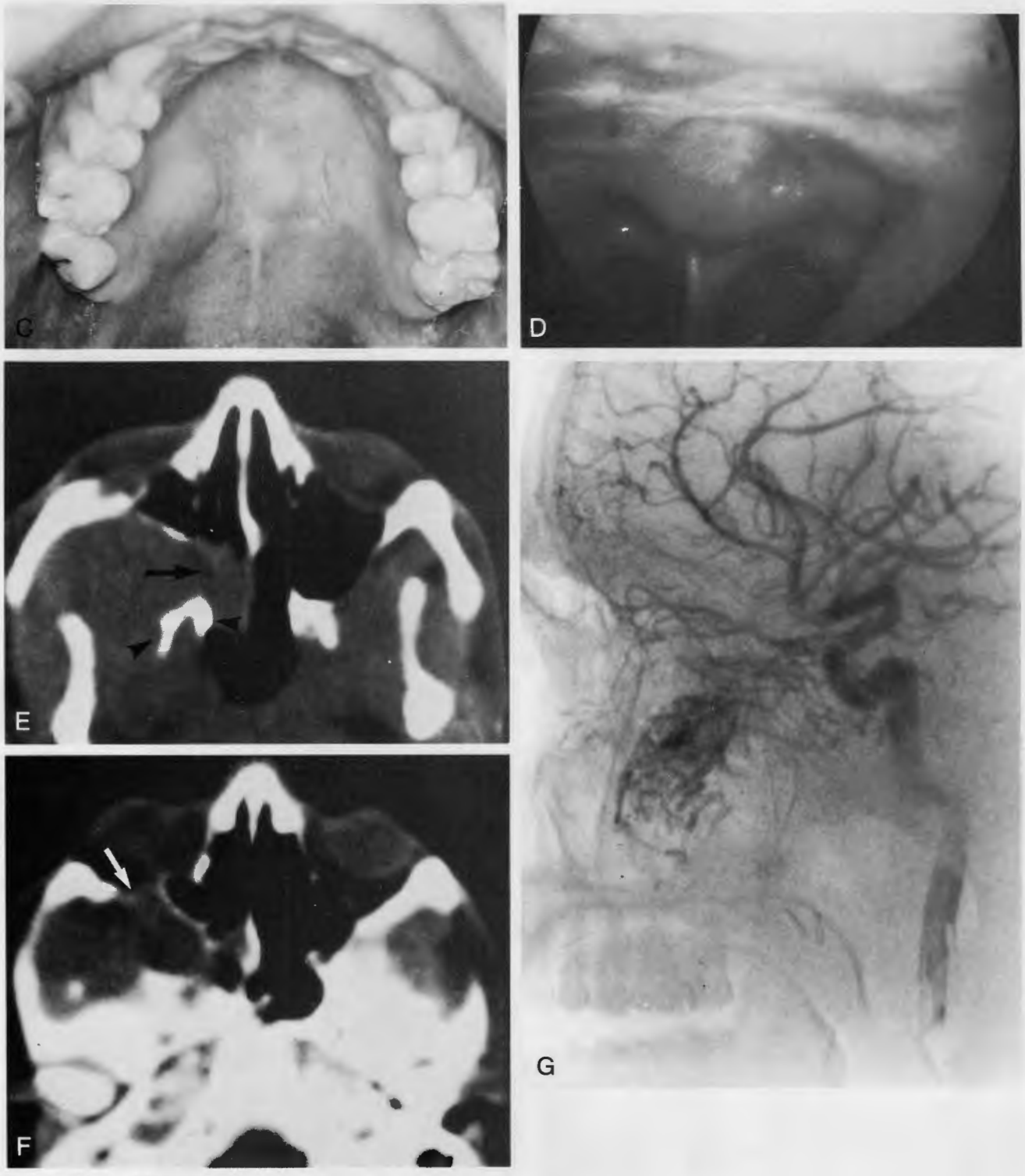

Figure 24-7. (*Continued*)

Figure 24-7. (*Continued*)

Figure 24-7. (*Continued*)

seven patients who had a second course of radiation therapy (3500 cGy over 3 weeks) with control of the lesion after the first course of radiation therapy had failed. The most common cause for failure of radiation therapy is inadequate volume rather than inadequate dosage.

Recurrence after surgery may be managed by repeat operation, but radiation therapy is frequently selected because of the tumor location.

RESULTS OF TREATMENT

Operative Results

Bremer and associates reported the surgical results from the Mayo Clinic, 1945 to 1983, for 150 patients with JAF. Specifically, 29 patients who had lateral rhinotomy between 1972 and 1983 were compared with 56 patients treated in a similar fashion between 1945 and 1971.[2] In the earlier group there was a 25% recurrence rate as compared with 17% in the more recent group. The mean blood replacement volume was 1400 mL, but preoperative embolization was rarely used. In the recent experience, no operative deaths occurred, as compared with five deaths in the earlier group. At the time of the analysis, 27 of the 29 recent patients were alive and free of disease.

Biller and coworkers reported results of 43 male patients with JAF seen over a period of 34 years at the Barnes Hospital in St. Louis.[1] Before 1965, 26 patients were treated surgically with a variety of surgical approaches. Tumor persisted in 16 of 26 patients (61%). Sixteen patients were operated on after 1965, and six patients had evidence of persistent tumor (37%). Five of the six patients with persistent tumor were rendered free of disease with secondary treatment with either radiation therapy or reexcision. Sequelae and complications were not reported.

Economou and colleagues reported 68 patients treated surgically.[8] The majority of the tumors were removed transpalatally. Symptomatic recurrences were noted in 16 patients with 12 going on to require two or more operations. Ultimately, 11 of 12 were asymptomatic. The remaining four recurrences were treated with radiation therapy. Eventually 92% of the surgical cases were cured. Embolization was used frequently, resulting in an average blood loss of 1 L. Radiation therapy was recommended for tumors with intracranial extension into the anterior and middle cranial fossae with parasellar feeding vessels because of the substantial operative risk.

Duvall and Moreano reported on 31 patients who had planned, comprehensive surgical excision.[7] Eight patients (26%) developed a recurrence, but all were free of disease after a second operation or estrogen.

Radiation Therapy Results

Jereb and coworkers reported the results for 69 patients with JAF treated between 1919 and 1966 at the Radiumhemmet in Stockholm.[12] Three patients were treated by surgery alone, 16 by surgery plus radiation therapy, and the remaining 50 by radiation therapy alone. The doses varied from 2000 to 6000 cGy. Of the 63 evaluable patients with at least a 5-year follow-up, 47 were free of disease from 10 years to longer than 40 years, 10 patients were free of disease for more than 5 years, and 6 for more than 1 year. No evidence of malignant disease occurred in any of the patients. Two patients died of treatment complications: one at the time of operation and the second of chronic osteitis and meningitis at the age of 51 after multiple courses of radiation therapy. Cataracts were noted in 2 patients.

Cummings and associates reported the results of Princess Margaret Hospital for 55 patients treated by radiation therapy.[6] Forty-two had no prior therapy and 13 had recurrent tumors after one or more operations. Follow-up was 3 to 26 years (greater than 5 years in 47 patients, greater than 10 years in 28 patients). The dose was 3000 to 3500 cGy over 3 weeks. The initial control rate was 80% and was the same for both dose schedules. The control rate was 83% in the group with no prior treatment and 69% in those recurrent after surgery. Five of the

recurrences were treated surgically, and three were controlled. Eight recurrent tumors were reirradiated, and all were controlled.

Nine patients were treated by irradiation at the University of Florida with follow-up from 3 to 14 years. Eight patients had involvement of the base of skull, seven had intracranial extension, and seven had had one or more prior surgical excisions. No patient had a recurrence, and no acute or late complications were identified.

FOLLOW-UP POLICY

Patients are seen at 1- to 3-month intervals for 3 years after surgery or radiation therapy. Follow-up is continued indefinitely in irradiated patients to watch for new neoplasms. MRI is preferred because intravenous contrast medium is not required, multiplanar imaging is simpler, and bone detail is usually not a critical feature of interest.

COMPLICATIONS OF TREATMENT

Radiation Therapy

At a dose level of 3000 to 3500 cGy over 4 weeks, one would expect temporary xerostomia, but most patients will have full return of their saliva. If the orbital contents are included, the possibility of cataract exists. Usually only the posterior orbit need be included in the treatment field, and the risk of eye complications is small (see Chap. 13).

The risk of radiation-induced neoplasms is estimated at 1 in 150 patients irradiated between the ages of 10 to 18 years and 1 in 400 for those older than 18 years.[5]

Repeat treatment to total doses of 5000 to 6000 cGy will produce complications similar to those seen for carcinoma of the nasopharynx (see Chap. 23).

Sixty-nine patients with JAF were treated between 1919 and 1966 at the Radiumhemmet, Stockholm, with follow-up from 1 to more than 40 years. In the earlier years, rather large doses of radiation were used; in more recent years, doses in the range of 2000 to 3000 cGy have been used. With the higher doses of radiation and long-term follow-up, the side effects were similar to those seen for treatment of carcinoma of the nasopharynx.[12]

Conley and associates reported two cases of serious radiation complications: osteoradionecrosis of the maxilla in one case and extensive radiation-induced squamous cell carcinoma of the skin developing 18 years after 12,000 R (orthovoltage).[4]

Surgery

Conley and coworkers reported the surgical complications for 55 operative procedures on 34 patients with JAF; 13 of the patients had recurrent disease when first seen.[4] Complications included severe bleeding after biopsy, persistent palatal fistula, temporary cardiac arrest, meningismus, dacryocystitis, hepatitis, and nephritis. Many of the complications occurred in the years 1940 through 1960, and complications have since decreased in frequency and severity.

Complications of lateral rhinotomy include nasal crusting and sequestra; obstruction of the nasolacrimal duct; hemorrhage; neurologic changes consisting of diplopia, obstructive deafness, and cheek numbness; serous otitis; perforation of the nasal septum; oral-antral fistula; and cerebrospinal fluid leak and meningitis.[2,17]

The transpalatal approach is associated with a small incidence of palatal dehiscence and rhinolalia, as reported by Economou and associates.[8] Other potential complications associated with the resection of more extensive lesions are cerebrospinal fluid leak, stroke, and death.

Operative death has been reported; the risk is increased with intracranial extension and recurrent disease.[4,21]

The operative mortality has decreased with improvements in surgical technique, anesthesia, and preoperative imaging and embolization.

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25

CARCINOMA OF THE SKIN

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About 90% of skin carcinoma occurs in the head and neck area. The incidence in the United States is estimated to be 600,000 cases per year.[7] The risk for carcinoma of the skin increases in sunny climates. A low incidence occurs in dark-skinned people; a corresponding increase occurs in those with a fair, ruddy, Scotch–Irish complexion. Seventy-five percent of basal cell carcinomas in blacks occur in sun-exposed skin, contrasted to about a 90% rate in whites.[42] The mortality rate is about 1800 per year, or 0.45%.

Some conditions associated with carcinoma of the skin are listed below:

- Actinic exposure
- Ionizing radiation
- Scar (eg, burn scar)[55]
- Chronic draining of sinus or fistulous tract (eg, pilonidal sinus)
- Immune disorders
  - Chronic lymphocytic leukemia
  - Transplant patients[25]
  - Discoid lupus erythematosus[27]
- Chemicals:
  - Arsenicals (herbicides, pesticides)
  - Psoralens and ultraviolet light (PUVA) treatment for psoriasis[54]
  - Nitrates
  - Tars, oils, and paraffins
- Hereditary disorders
  - Xeroderma pigmentosum
  - Basal cell nevus syndrome
  - Albinism
  - Congenital epidermolysis bullosa[12]

ANATOMY

The epidermis is thinner in the face than in most portions of the body, measuring approximately 0.04 mm. No consistent change in the thickness of the epidermis occurs with increasing age, and no difference in skin thickness exists between men and women.

The dermis, which contains the blood and lymphatic vessels, adnexa, hair follicles, sweat glands, and sebaceous glands, is 1 to 2 mm thick; the dermis of the eyelid is thinner, 0.6 mm or less. Beneath the dermis lies the subcutaneous tissues containing the fat and the superficial fascia. No distinct transition occurs from the dermis to the subcutaneous layer.

Lymphatics

No lymphatics exist in the epidermis. A superficial capillary lymphatic plexus lies in the dermis and is without valves.[61] The deep lymphatic trunks in the dermis and subcutaneous tissues have valves. The density of the capillary lymphatics has been noted to be about the same in all areas, except the sole of the foot and palm of the hand, where it is denser. Observation suggests that squamous cell carcinomas and malignant melanomas occurring on the skin of the temple are particularly prone to develop lymphatic metastasis.[56]

During the healing of wounds such as incisions or burns, a regeneration of lymphatic capillaries across the scar occurs, similar to the regrowth of small blood vessels.[61]

The first-echelon lymph nodes for carcinomas of the face and scalp are the superficial network of lymph nodes that form a ring around the top of the neck: submental, submandibular, parotid area, postauricular (mastoid), and occipital lymph nodes, as well as inconstant facial lymph nodes. (See Chap. 6, section on anatomy of the head and neck lymphatic system, and Chap. 27 for additional discussion regarding lymphatics.)

PATHOLOGY

The most common carcinomas of the skin are basal cell carcinoma (65%), squamous cell carcinoma (30%), or one of their variants, and the adnexal carcinomas. Merkel cell carcinoma is a rare neuroendocrine malignancy arising in the skin that was first described by Toker in 1972.[57] Verrucous carcinoma, a variant of squamous cell carcinoma, occurs most often on the foot and is rare in the head and neck area. Carcinoma in situ occurs frequently in the head and neck. Any of the carcinomas may show perineural invasion, particularly with recurrent disease.

Carcinomas (eg, renal cell carcinoma) originating outside the head and neck area may metastasize to the skin, especially the scalp.

Basal Cell Carcinoma

The common basal cell carcinoma, which arises from the basal layer of the epithelium, may have a variety of growth patterns merge into one another in the same tumor, and the different names applied to the gross and microscopic appearances have clinical implications. The morphea type (sclerosing basal cell carcinoma) shows little surface disease and a marked infiltrative picture; it is an important subtype because of the higher risk for recurrence. Microcystic basal cell carcinoma is a histologic variant of basal cell carcinoma that exhibits the same natural history as the more common variety. Some lesions will have mixed basal cell and squamous cell carcinoma (basosquamous cell carcinoma or metatypical basal cell carcinoma).

Melanin pigment may be seen on both gross and microscopic examination of basal cell carcinoma.

Squamous Cell Carcinoma

Squamous cell carcinoma and its variants (ie, verrucous carcinoma, spindle cell squamous carcinoma) are similar histologically to squamous cell carcinomas occurring in other sites. Most are well differentiated, but a small number are poorly differentiated. Evans and Smith[13] identified two categories of spindle cell tumors of skin: one group was composed of squamous cell carcinoma mixed with a spindle cell component; the other was predominantly spindle cells. The spindle cell component was similar in both groups; mitoses, giant cells, and epithelioid cells may be seen.

Keratoacanthoma

Keratoacanthoma is a benign tumor of the skin that grossly resembles a cystic basal cell carcinoma and microscopically resembles squamous cell carcinoma or squamous papilloma. Part of the difficulty in histologic diagnosis is due to an inadequate biopsy specimen. Ackerman[2] concluded that "the diagnosis of keratoacanthoma can only be made with absolute certainty by biologic behavior in the form of eventual involution."

Adnexal Carcinoma

Carcinomas may arise from the epithelium of the sweat glands, sebaceous glands, or hair follicles, and microscopically resemble the tissue of origin. Carcinoma of the sweat gland can arise from either the eccrine or apocrine glands, but no reliable histologic criteria exist to differentiate the origin. It is difficult to distinguish between benign and malignant carcinoma of the sweat gland in the absence of metastases. The differential diagnosis includes adenocarcinoma metastatic to skin, and basal cell and squamous cell carcinomas with an adenoid cystic growth pattern. They are frequently misdiagnosed at the time of the first biopsy. Malignant tricholemmoma arising from hair follicles is extremely rare.

Microcystic adnexal carcinoma (sclerosing sweat duct carcinoma) is a rare variant of adnexal carcinoma, first described in 1982. The lesion usually presents on the upper lip or skin of the periorbital area as an indurated plaque without direct invasion of the overlying epidermis. It tends to be slow growing and locally invasive.[10,35,46] Microcystic adnexal carcinoma exhibits a propensity for local recurrence after excision and is associated with perineural invasion; lymph node metastases are rare. The role of radiation therapy in the treatment of this rare malignancy is undefined.

Merkel Cell Carcinoma

Merkel cell carcinoma is a small cell neuroendocrine carcinoma arising in the skin. As in neuroendocrine carcinomas arising in other primary sites, Merkel cell carcinoma produces neuron-specific enolase and has been found to contain membrane-bound neurosecretory granules within the tumor cells. In the past, the correct diagnosis often was not obtained until an extensive recurrence was noted. Merkel cell carcinoma was often misdiagnosed as basal cell carcinoma, lymphoma, adnexal carcinoma, or carcinoma metastatic to the skin from another primary site (ie, small cell carcinoma of the lung or medullary carcinoma of the thyroid).[18]

Dermatofibrosarcoma Protuberans

See Chapter 33 for a discussion of dermatofibrosarcoma protuberans.

PATTERNS OF SPREAD

The patterns of spread for individual anatomic sites are outlined in the section on selection of treatment by anatomic site. Some lesions remain confined to the epidermis (carcinoma in situ) and may involve a large area of skin. Large in situ lesions occur more often on the trunk, but small areas of in situ disease are common on the head and neck skin.

Basal Cell and Squamous Cell Carcinoma

Both basal cell and squamous cell carcinomas usually are well differentiated, and most have an indolent growth with distinct, "pushing" margins; a small proportion are poorly differentiated and grow rapidly. Basal cell carcinoma occurs more frequently around the central portion of the face, whereas squamous cell carcinoma occurs more often on the ears, preauricular and temporal area, scalp, and skin of the neck.

Most lesions remain superficial and invade the adjacent epidermis in a circumferential growth pattern. Invasion of the dermis usually is confined to the superficial (papillary) dermis. Eventually penetration of the reticular dermis, subcutaneous tissues, and other underlying structures occurs. A few skin carcinomas tend to grow beneath the skin, and the surface lesion gives little indication of their extensive growth; this is more often seen in recurrent tumors. The great majority of early basal cell and squamous cell carcinomas show an orderly invasion of the superficial dermis, which allows successful local therapy. Both basal cell and squamous cell carcinomas invade cartilage and bone, develop perineural spread, and eventually enter the lymphatics, although the latter is not common. Basal cell carcinoma, in particular, has a low incidence of lymphatic involvement unless it is recurrent, whereas the incidence of lymph node spread for squamous cell carcinoma is estimated to be 10% to 15%.

Scanlon and coworkers[49] suggested the possibility that a small proportion of basal cell carcinomas spread along interstitial tissue planes and develop satellites.

Squamous cell carcinomas may develop distant metastasis, whereas basal cell carcinomas rarely produce metastasis.

Metatypical basal cell carcinoma is intermediate between basal cell carcinoma and squamous cell carcinoma as far as recurrence rates and risk of metastases.[50]

Spindle cell tumors of the skin have a gross appearance and growth pattern similar to squamous cell carcinomas.

Carcinoma of the Sweat Gland

Carcinoma of the sweat gland occurs with equal frequency in males and females. It predominantly affects elderly people, but it may occur even in early adulthood. The lesion is generally a subcutaneous nodular mass, which may be solitary or multiple, and the larger lesions may be ulcerated. Carcinoma of the sweat gland most often occurs on the eyelid, face, and scalp. The growth rate varies from indolent to rapid. The tumor may be present for several years with little change, and then suddenly may begin to enlarge. Perineural invasion is frequent. Regional and distant metastases may develop. The scalp lesions are the ones most likely to develop metastases to regional lymph nodes.

Recurrence after excision is frequent, and often multiple recurrences are reported.[14,22] Little information exists on the response to radiation therapy.[22] In our limited experience, carcinoma of the sweat gland is sufficiently radioresponsive to justify irradiation, particularly in association with excision.

The mucin-producing sweat gland adenocarcinoma is a rare tumor: 47 cases had been reported to 1978. The eyelid is the primary site in about half of the cases, and the face and scalp in another one fourth of the cases. The tumor presents most often in middle-aged men. Wright and Font[60] reported 21 cases that originated on the eyelid. Eight patients (38%) developed one or more local recurrences, one died with extensive persistent disease in the face after a 15-year interval, and only one patient had metastasis to the submandibular lymph nodes successfully treated by radical neck dissection. Regional or distant metastasis is a relatively infrequent event for lesions arising in the head and neck area.

Sebaceous Gland Carcinoma

Sebaceous gland carcinoma is rare. It occurs most often on the eyelids, predominantly on the upper lid in elderly women, but the lower lid and caruncle are also sites of origin; it may occur on other parts of the head and neck skin. It is often indolent in its growth, but it may be locally aggressive and develop regional and distant metastases. Local recurrence is common after excision because the lesions often have significant deep and lateral spread beyond the obvious lesion. Metastasis to regional lymph nodes is reported in about 20% of cases, and a small percentage of patients develop distant metastasis.[37] Inadequate treatment often occurs because of incorrect histologic diagnosis.

Keratoacanthoma

This benign lesion starts as a firm, round skin nodule and grows to 1 to 2 cm in a short time, usually a few weeks. As the lesion matures, the center becomes separate and can be removed, revealing a small crater. The lesion occurs most often in the exposed areas of the head and neck. Keratoacanthoma is an unlikely diagnosis for a lesion of the lip vermilion. Typically, keratoacanthoma undergoes spontaneous regression. Conversion to squamous cell carcinoma is a controversial point because the lesions resemble squamous cell carcinoma in the beginning. Fitzpatrick and Harwood[15] have described an aggressive variant of squamous cell carcinoma of the skin that displays a rapid growth pattern and may mimic keratoacanthoma. Keratoacanthoma is twice as common in men as women. It occurs most often in patients older than 40 years of age, but it may be seen as early as the second decade.

Basal Cell Nevus Syndrome

The basal cell nevus syndrome is an autosomal-dominant disorder with a high level of penetrance, but a variable clinical picture. The clinical syndrome may be composed of any or all of the following:

- Multiple basal cell carcinomas (differing only in their tendency to develop at an early age and on unexposed skin areas)
- Jaw cysts (common)
- Palmar or plantar pits
- Skeletal abnormalities (short fingers, hypertelorism)
- Ectopic calcification
- Eye muscle palsies
- Hamartomas
- Epidermal cysts (milia)

The age at onset is frequently in the second or third decade, and a family history is often positive for the disorder.[53]

Merkel Cell Carcinoma

Merkel cell carcinoma occurs primarily in white men between 60 and 80 years of age.[18] The lesion often presents as a painless, raised skin nodule or mass that is red, pink, or blue and may have diffuse margins, and is covered with an intact epidermis. Most lesions are 2 cm in size at diagnosis.[18] About half of patients diagnosed with Merkel cell carcinoma have a primary lesion in the head or neck.[52] Most head and neck Merkel cell carcinomas occur on the skin of the cheek, upper neck, and nose.[18]

Merkel cell carcinoma displays an aggressive growth pattern. Goepfert and coworkers[18] reported that regional lymph nodes of 45% of patients were clinically positive; most commonly the ipsilateral parotid, submandibular, or upper jugular nodes were involved. They noted that 19 of 23 patients (83%) with primary lesions less than 2 cm in size developed lymph node metastasis at some point in the disease process. Distant metastases were noted in 48% of patients in the M.D. Anderson series (Houston); one patient had distant metastasis on admission, and the remaining patients developed metastases within 2 to 47 months (79% within 18 months) of treatment. The likelihood of distant metastasis correlated with disease control above the clavicles: 2 of 12 patients (17%) who remained disease–free above the clavicles developed distant metastasis, compared with 11 of 16 (69%) who experienced disease recurrence above the clavicles.[18] As has been observed in small cell carcinoma of the lung, Merkel cell carcinomas may produce various hormones such as adrenocorticotropic hormone.

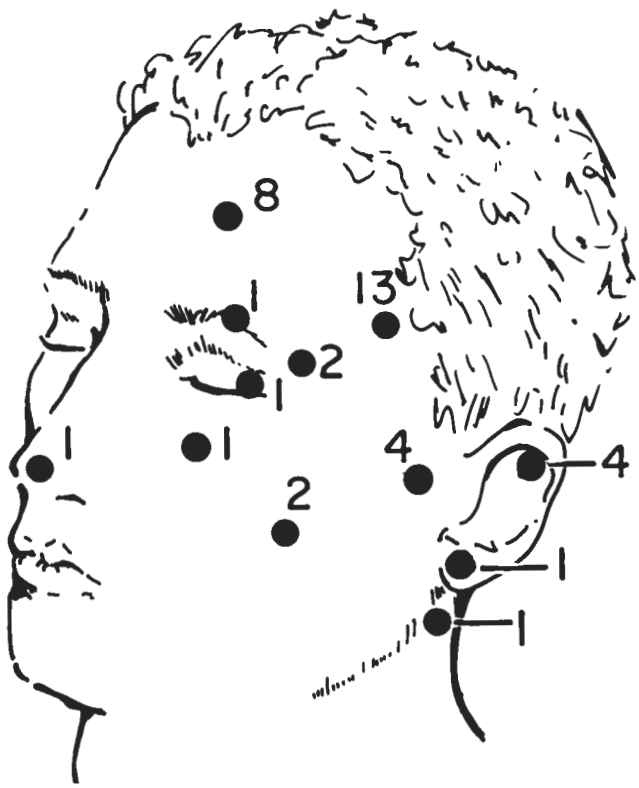

Figure 25-1. Sites of skin cancer judged to account for the parotid-area metastases. In three patients with multiple lesions, the site of the primary tumor was not determined. Two patients had no history of previous skin cancer. Fifty-five patients are represented on the diagram. (Taylor BW, Brant TA, Mendenhall NP, Mendenhall WM, Cassisi NJ, Stringer SP, Million RR. Carcinoma of the skin metastatic to parotid area lymph nodes. Head Neck 1991;13:428)

Lymphatics

The overall risk of lymphatic metastases is estimated to be 10% to 15% for squamous cell carcinoma of the skin. The risk increases with the size of the lesion, depth of penetration, histologic grade, and recurrence.

Jackson and Ballantyne[26] reviewed the M.D. Anderson Hospital experience in the management of skin cancer metastatic to lymph nodes of the parotid area. The incidence of clinically positive lymph nodes in the ipsilateral neck was 24% for 149 nonbasal cell carcinomas, and 21% gave positive pathologic results. Disease incidence in the clinically negative neck was 24% with elective neck dissection.

The skin site of origin for squamous cell carcinoma of the skin metastatic to lymph nodes of the parotid area, from the University of Florida (Gainesville), is shown in Figure 25-1.[56] Regarding patients for whom information on node location was available, 74% had involved lymph nodes anterior to the ear (either the superficial preauricular or the parotid nodes), 22% had involvement of the tail of parotid lymph nodes, and 4% had both.[56] Internal jugular nodes with positive clinical findings were noted in 4 of 54 cases. The preauricular lymph nodes may be small when first involved and easily missed unless a careful examination is carried out. Lesions arising from the temple area seem to have a high risk for lymph node metastases, but it is unknown whether this is related to a rich capillary lymphatic supply or to the size and depth of invasion.

The risk for lymph node metastases from previously untreated basal cell carcinomas is less than 1% and is not related to size, depth of penetration, or histologic subtype; the risk increases for recurrent basal cell carcinomas, especially those with multiple recurrences over several years. Lymph node metastases, however, are seen on rare occasions without a history of recurrence, and an interval of several years may occur between the treatment of the primary lesion and the appearance of involvement in lymph nodes. When they do occur, lymph node metastases often are solitary.

Lesions of the posterior scalp spread to the occipital nodes; lesions of the parietal area spread to the postauricular nodes; lesions of the frontal scalp, temple, and eyelids spread to lymph nodes of the parotid area; and lesions around the nose and lips spread to the submandibular and parotid areas. The tiny buccal, facial, and mental foramen nodes, and other inconstant intercalated lymph nodes near the nasolabial fold and lateral canthus, are less common sites of lymph node metastasis and often are missed due to failure to look for them or recognize them when seen or palpated. Lesions that occur in overlapping lymphatic areas may spread in either or both directions.

When first involved, the superficial lymph nodes frequently are small and easily missed unless thorough, gentle examination is carried out. This is particularly true for the tail of parotid and superficial preauricular lymph nodes, which are the most commonly involved lymph nodes from skin cancer.

All of the first-echelon lymph nodes eventually drain to the internal jugular chain or spinal accessory chain lymph nodes.

CLINICAL PICTURE

Presenting Symptoms

The common history for basal cell carcinoma or squamous cell carcinoma is a slowly enlarging growth on or just beneath the skin surface. Often a history exists of a sore that will not completely heal. Other symptoms such as bleeding or pain are unusual until the lesion becomes large, and even then symptoms are relatively mild and infrequent. Patients with perineural spread may complain of paresthesia, especially the sensation of worms crawling under the skin. We have observed several cases that spread centrally along the facial nerve or branch of the trigeminal nerve (ie, infraorbital nerve), eventually producing multiple cranial nerve palsies and destruction of the apex of the temporal bone and floor of the middle cranial fossa. The diagnosis was delayed because the physicians did not associate the history of skin cancer and the possibility of tumor tracking along nerve sheaths to colonize a more central location. Advanced, neglected lesions with bone and cartilage destruction, orbit invasion, and regional metastases are still seen; these advanced lesions often produce few, if any, symptoms, and patients simply delay consulting a physician.

Physical Examination

The regional lymph nodes must be carefully examined, even though they are not often involved. Because of the infrequent appearance of regional lymphatic metastases, and because cases of skin cancer often are not followed diligently, lymph node metastases frequently are missed. Although lymphatic metastases may appear within a few months of the management of the primary lesion, in some cases many years intervene before the regional lymph nodes become apparent. It is not at all unusual for 5 years or more to intervene between the primary lesion and the appearance of metastasis. Patients with chronic lymphocytic leukemia and concomitant skin cancer often have enlarged lymph nodes from both processes and may have elements of squamous cell carcinoma and leukemia in the same lymph nodes.

When the lymph nodes in the preauricular area become involved, especially when a latent period of several years occurs between treatment of the primary squamous cell carcinoma and the appearance of a metastatic node, they are frequently misdiagnosed as squamous cell carcinoma originating in the parotid gland. Failure to recognize their true origin results in inappropriate and unsuccessful treatment in most cases. *Squamous cell carcinomas (or adnexal carcinomas) arising from the temple area seem to have an especially high risk for lymphatic metastasis.* Patients with these particular lesions should be watched carefully.

METHODS OF DIAGNOSIS AND STAGING

Biopsy should be performed on the majority of lesions before deciding on treatment. We do not always insist on biopsy for elderly patients who have a typical skin carcinoma and are to be treated by radiation therapy.

Small lesions occurring on the free skin areas (ie, not involving the eyelid, ear, or periorbital areas) usually can undergo biopsy and be treated simultaneously with surgical excision. Larger lesions, or those involving areas where functional or cosmetic deficit might occur from excision, first undergo biopsy with a small incisional biopsy or with a skin punch. Biopsy with a skin punch should include the subcutaneous fat; punch biopsy is contraindicated when differentiating between keratoacanthoma and squamous cell carcinoma because of the small sample size.

The following is a partial list of conditions to be considered in the differential diagnosis of basal cell carcinoma and squamous cell carcinoma:

- Senile keratosis
- Keratoacanthoma
- Nonpigmented nevi
- Malignant melanoma
- Cutaneous horn
- Psoriasis
- Lymphoma (mycosis fungoides)
- Soft tissue sarcomas (dermatofibrosarcoma protuberans)
- Hemangiosarcoma
- Metastatic carcinoma
- Adnexal carcinoma of skin
- Merkel cell carcinoma

Staging

The 1988 American Joint Committee on Cancer staging is based on size of the tumor and involvement of muscle, bone, nerve, or cartilage[4]:

TX:	Minimum requirements to assess the primary tumor cannot be met
Tis:	Preinvasive carcinoma (carcinoma in situ)
T0:	No primary tumor present
T1:	Tumor 2 cm or less in its largest dimension
T2:	Tumor more than 2 cm but no more than 5 cm in its largest dimension
T3:	Tumor more than 5 cm in its largest dimension
T4:	Tumor involving other structures such as cartilage, muscle, bone, or nerve

Neck node staging is the same as for other head and neck sites (see Chap. 6).

Diagnostic Imaging

Computed tomography (CT) and magnetic resonance imaging (MRI) are only necessary in a carefully chosen group of patients being treated for skin cancer. CT is the primary modality for showing bone invasion and nodal metastases. High-resolution MRI is potentially better than CT for demonstrating perineural spread of tumor.[32]

Imaging of the Normal Anatomy

Normal anatomy relevant to evaluating skin cancer is discussed in several chapters, including Chapters 16, 22, 27, and 29. Evaluation of facial, cervical, and parotid region nodes is discussed in Chapters 6 and 27.

Techniques of Examination

The general techniques used for CT and MRI of the head and neck are presented in Chapter 4. These are applied according to the site of origin of the skin carcinoma; the site-specific technical details are presented in appropriate chapters (see Chap. 29, section on diagnostic imaging). The techniques used for study of the parotid, facial, and cervical nodes are presented in Chapters 4 and 27.

It is extremely important to ensure that the plane of section, spatial resolution, and use of intravenous contrast are fully optimized when searching for perineural spread of skin carcinoma. Whenever branches of the trigeminal nerve are involved, the study should include the cavernous sinus and brain stem. Likewise, when the facial nerve is at risk, its entire course from the face to the parotid, through the temporal bone, and on to the brain stem *must* be studied (see Chap. 4, Figs. 4-10*A* and *B*). Good basic imaging of cranial nerves at risk requires that the study *always include the entire course of the nerve* from its nucleus of origin to its end organ.

When bone invasion is suspected, CT images *must* be processed for both bone and soft tissue detail and viewed carefully at optimal window settings. Subtle abnormalities should be confirmed in two planes whenever feasible.

Indications for Imaging

The main indications for imaging with CT and MRI in patients with skin cancer include the following:

DETERMINATION OF THE DEEP EXTENT OF SOFT TISSUE INVOLVEMENT. MRI is more definitive than CT for showing invasion of deep muscles (eg, temporalis, masseter) (Fig. 25-2). A potential exists for tumor invasion into fat or bone containing fatty marrow to be obscured on MRI done with intravenous paramagnetic contrast. This pitfall is discussed in Chapter 4.

DETECTION OF BONE INVASION. CT is clearly better than MRI for detecting bone invasion (Fig. 25-3). Moreover, CT can *exclude* bone invasion, especially early cortical erosion, with a much higher degree of confidence than MRI. MRI often shows the spread of tumor within the marrow spaces of bone and early spread beyond bone to dura better than CT (see Chap. 4, Fig. 4-3).

DETECTION OF PERINEURAL SPREAD OF TUMOR. Both CT and MRI are capable of detecting perineural spread (see Figs. 25-3 and 25-4). The findings can be subtle on both studies, and a thorough knowledge of the anatomy surrounding the course of the nerve in question is required when trying to diagnose or exclude perineural spread of skin cancer. Either study can produce negative results when the tumor fails to enlarge the nerve. MRI can show enlargement and enhancement of inflamed nerves mimicking tumoral enlargement (see Chap. 4, Fig. 4-10*C*). The cranial nerves are surrounded by a rich vascular plexus near their exit foramina and often beyond that; the resulting normal perineural enhancement can be misdiagnosed as tumor by inexperienced observers.

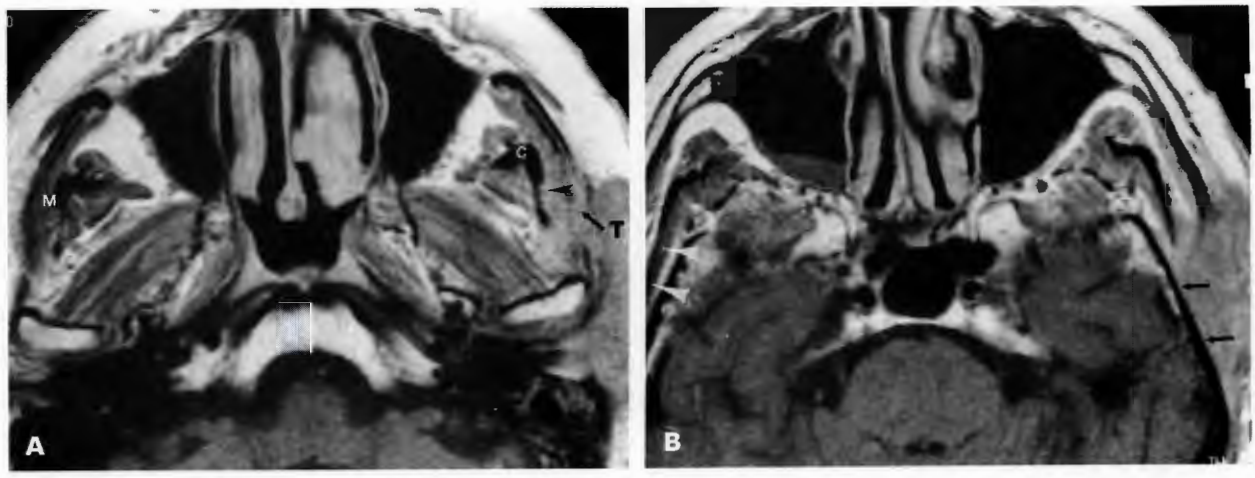

Figure 25-2. A patient with squamous cell carcinoma involving the temporal and upper periparotid region. (*A*) T1-weighted MRI with injection of paramagnetic contrast medium, made at the level of the zygomatic arches. Tumor (T) infiltrates the attachments of the masseter muscle to both the zygomatic arch (*arrow*) and the mandible (*arrowhead*) adjacent to the coronoid process (C); note the normal appearance of the masseter muscle (M) on the opposite side. (*B*) A section approximately 1 cm higher than that seen in *A* shows the tumor invading the temporalis muscle and deeper layers of the scalp down to the cortex of the squamous portion of the temporal bone (*arrows*); compare this with the normal temporalis and other deep soft tissues are seen on the opposite side (*arrowheads*). CT (not shown) through this area revealed no bone erosion. Even though the cortical margin of the bone is sharp on MRI, CT was necessary to exclude bone erosion with a high degree of confidence.

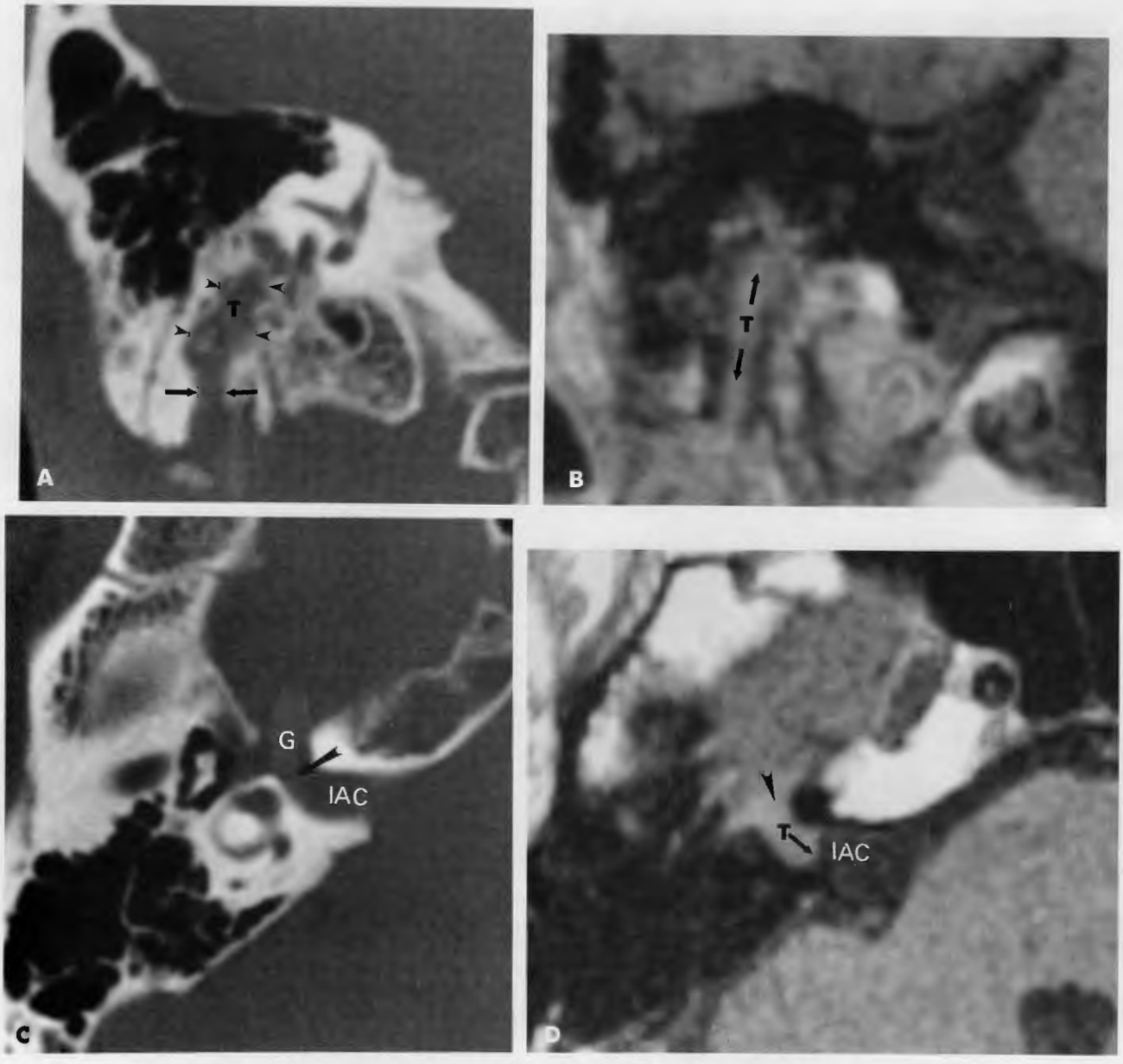

Figure 25-3. This patient had squamous cell carcinoma of the skin metastatic to parotid lymph nodes. The patient's carcinoma recurred after initial therapy. Symptoms associated with the recurrent tumor included paralysis of the facial nerve. (*A*) Coronal section from a CT scan made through the descending facial canal. The stylomastoid foramen (*arrows*) is at least two to three times larger than usual. The descending facial canal is widened to three to four times its normal size and its margins (*arrowheads*) are eroded by the tumor (T) extending along the facial nerve. (*B*) T1-weighted coronal MRI section matching the coronal CT scan seen in *A*. The tumor (T) infiltrating the facial nerve (*arrows*) can be seen, but it is difficult to appreciate the anatomy of the bony facial canal; in fact, without the opposite side for comparison, it is difficult to realize that the nerve was so abnormal on the basis of this image alone. (*C*) An axial CT section made through the level of the geniculate ganglion (G) and internal auditory canal (IAC). The bony facial canal in the region of the geniculate ganglion and labyrinthine segment of the facial nerve (*arrow*) is noticeably widened by tumor spreading along the nerve. The tumor itself is not seen. (*D*) Axial MRI section done after injection of paramagnetic contrast medium at a level matching that of the CT section in *C*. Tumor (T) is seen at the level of the geniculate ganglion (*arrowhead*) and within the IAC (*arrow*). Note how the CT and MRI information are complementary in this patient; CT shows the bone erosion far better than MRI, and MRI shows the extent along the facial nerve more precisely than CT.

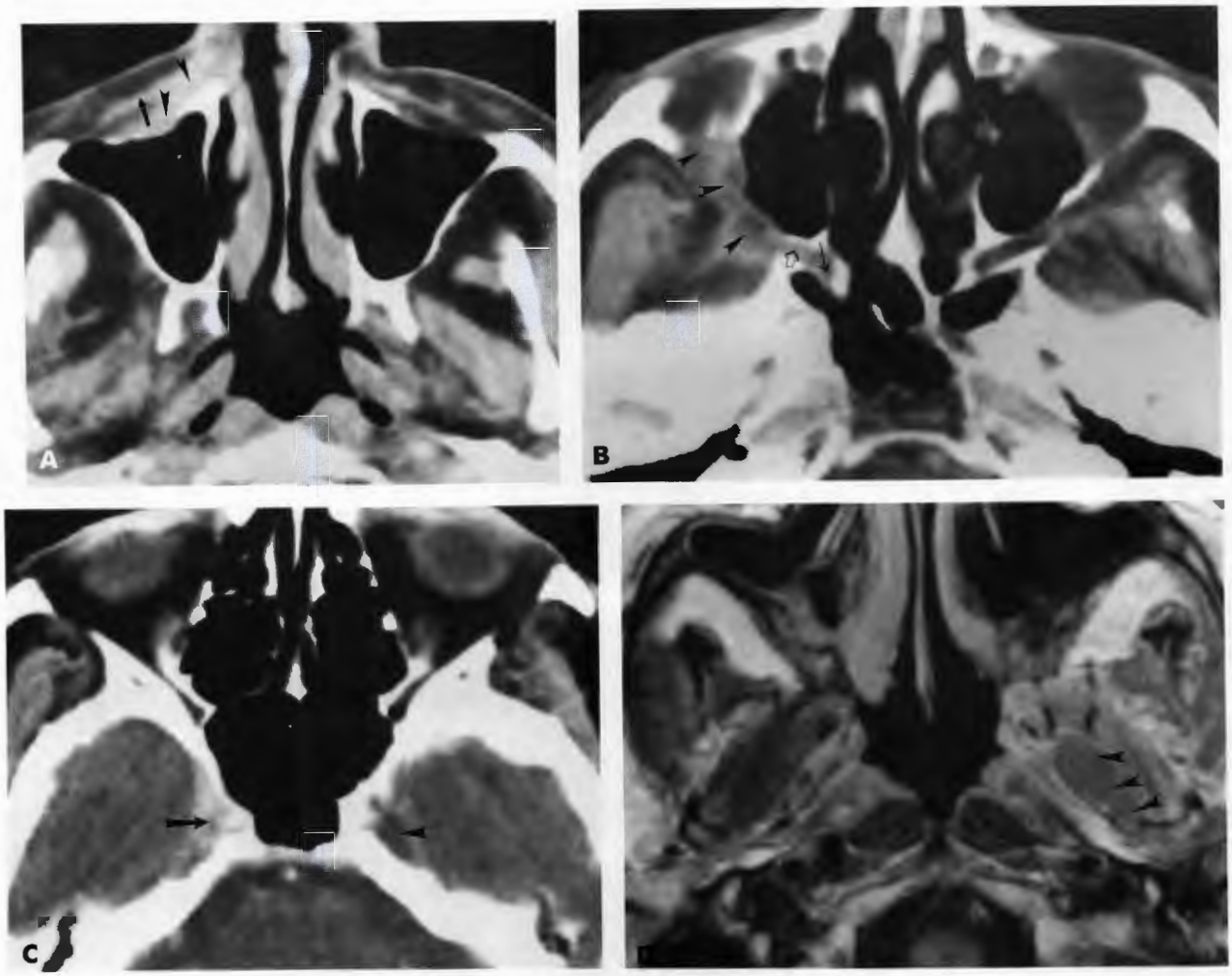

Figure 25-4. This patient had surgery for multiple recurrences of squamous cell carcinoma involving the nasolabial fold region. He then developed numbness and tingling in the distribution of the maxillary nerve. No visible or palpable mass was present at the primary site, but the physical examination was somewhat compromised by scarring from prior surgery. (*A*) Axial CT shows thickening of the soft tissues (*arrowheads*), which is primarily deep to the muscles of facial expression (*arrow*) and infiltrating the fat adjacent to the anterior wall of the maxillary sinus; compare with normal side. (*B*) Axial CT made approximately 1 cm cephalad to that in *A*. Tumor spreads along the course of the infraorbital nerve (*arrowheads*) to the pterygopalatine fossa (*open arrow*) and then to the opening of the foramen rotundum (*arrow*). Compare the nodular thickening along the course of the infraorbital nerve with the normal anatomy in the same region on the opposite side. (*C*) Contrast-enhanced CT made approximately 5 mm cephalad to that seen in *B*. Meckel's cave is obliterated on the side of tumor (*arrow*) compared with its normal cerebrospinal fluid density counterpart on the normal side (*arrowhead*). This finding strongly indicates tumor involving the trigeminal nerve back to the ganglion. (*D* and *E*) A different patient than seen in *A* through *C*. Two additional images from the patient shown here are presented in Figures 4-10*A* and *B*. He had a history of recurrent squamous cell carcinoma of the pinna. The tumor initially had extended along the facial nerve. After surgery and radiation therapy for that recurrence, the patient developed facial pain in the distribution of the mandibular nerve and also had pain in the periauricular region. (*D*) MRI showed marked thickening of the mandibular nerve (*arrowheads*); compare with normal anatomy on the opposite side. Lower sections (not shown) showed strong evidence of spread to the mandibular nerve along the expected position of the auriculotemporal nerve. (*E*) Axial MRI through the cavernous sinus after injection of paramagnetic contrast material shows tumor within the Meckel's cave (T), which also was growing along the maxillary nerve (*arrowheads*), and extended along the trigeminal nerve to involve the brain stem (*arrow*) at the root entry zone of the fifth nerve.

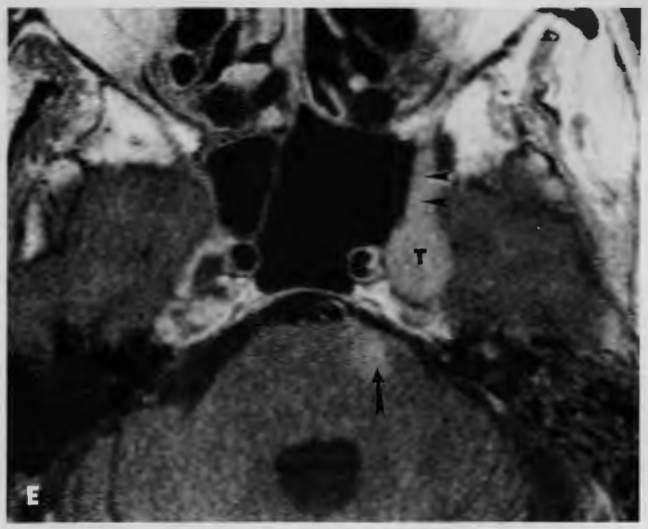

Figure 25-4. (*Continued*)

DETECTION OF RECURRENT DISEASE. Recurrent carcinoma of the skin frequently has a much deeper extent than can be appreciated on physical examination (see Fig. 25-2). Whenever the physical examination is inconclusive, MRI, CT, or both should be done. In this setting, the rate of detection of bone invasion, as well as clinically occult perineural spread and adenopathy, will increase.

DETECTION OF PAROTID, FACIAL, AND CERVICAL ADENOPATHY. See discussion in Chapter 6.

Patients suspected of having basal cell nevus syndrome should have appropriate radiographs to determine the extent of skeletal abnormalities.

TREATMENT

Treatment Modalities

A number of treatments are successful, including radiation therapy, a variety of surgical techniques, and topical chemotherapy; superficial basal cell carcinomas sometimes heal spontaneously.

Topical Chemotherapy

Topical chemotherapy, usually with 5-fluorouracil, is successful for superficial lesions that are confined to the epidermis, such as precancerous keratosis and carcinoma in situ. Topically applied 5-fluorouracil should not be used for invasive lesions since they appear to heal on the surface, allowing continued growth below the epidermis.[41] Invasive lesions treated with topical 5-fluorouracil have been observed to show temporary regression and then show an accelerated growth rate.

Surgical Techniques

Surgical techniques include scalpel excision, curettage and electrodesiccation, fulguration and curettage, cryotherapy, and chemosurgery. All of these techniques, when applied to appropriate lesions, are reported to produce excellent results in the hands of experienced clinicians.

CURETTAGE WITH ELECTROSURGERY. Curettage with electrosurgery is commonly used by the dermatologist and is successful. It is usually reserved for relatively small, superficial, well-defined lesions. The area is anesthetized, and a sharp curet is used to scrape away the lesion until normal tissue is reached. The base of the wound is electrodesiccated to ensure destruction of remaining tumor cells and to obtain hemostasis. The physician depends on sensations from the curet to determine when normal tissue is reached. The process is repeated for larger lesions. Lesions of the tip and ala of the nose, lip vermilion, periorbital areas, auriculotemporal fold, or any large or deeply invasive lesions are better treated by other means, since the cure rate, cosmetic result, and functional result may not be optimal. Although successful for small lesions, this technique provides no specimen for checking the adequacy of the margins, which would be important in larger tumors. Healing occurs by second intention with a flat white scar. Healing time, usually 2 to 4 weeks, is longer than for a simple excision. The scar may be noticeable if adjacent to darker skin.

ELECTROFULGURATION AND CURETTAGE. The area is anesthetized, and a diathermy unit is used to coagulate the lesion and adjacent normal tissue. The initial coagulum is removed with a curet, after which repeated electrocoagulation is performed until normal-appearing tissue is reached. The wound heals in an average of 5 weeks. The cosmetic appearance is satisfactory when a small lesion is treated in this manner. Recurrence usually appears on the surface of the scar and is said to be easily detected; but recurrence may develop in the tissues deep to the scar and may become extensive before appearing at the surface. No specimen is available to determine adequacy of margins.

MICROSCOPICALLY CONTROLLED EXCISION. In this technique, initially developed by Mohs,[41] the lesion is excised under microscopic control. The tumor is either fixed in situ with an application of zinc chloride paste (fixed-tissue technique), or excised without prior fixation (fresh-tissue technique). The fixed-tissue technique occasionally is used to resect deeply invasive skin cancer where bone invasion is suspected[23,41] (Fig. 25-5). It has been replaced, for the most part, by the fresh-tissue technique.

Fresh-Tissue Technique. The fresh-tissue technique is indicated for most cancer resected using Mohs' surgery and has the advantage of being more rapid and less painful than the fixed-tissue method. It usually can be accomplished in one procedure, whereas the fixed-tissue technique may require several days. The major difference in the two techniques is that the in situ fixation is omitted. Hemostasis is accomplished by the application of a thin layer of oxidized cellulose (Oxycel, Deseret Medical, Sandy, UT), superficial electrodesiccation, or the application of dichloroacetic acid. Ligatures are occasionally required. The wound usually is allowed to heal by secondary intention, or in some cases the defect is reconstructed immediately. This method adds an average of 2 hours to the surgical procedure, but allows the entire excision to be finished in 1 day.

Advantages and Disadvantages. The major advantage of microscopically controlled excision is the selective removal of tumor ramifications, which may extend a considerable distance in haphazard directions beyond

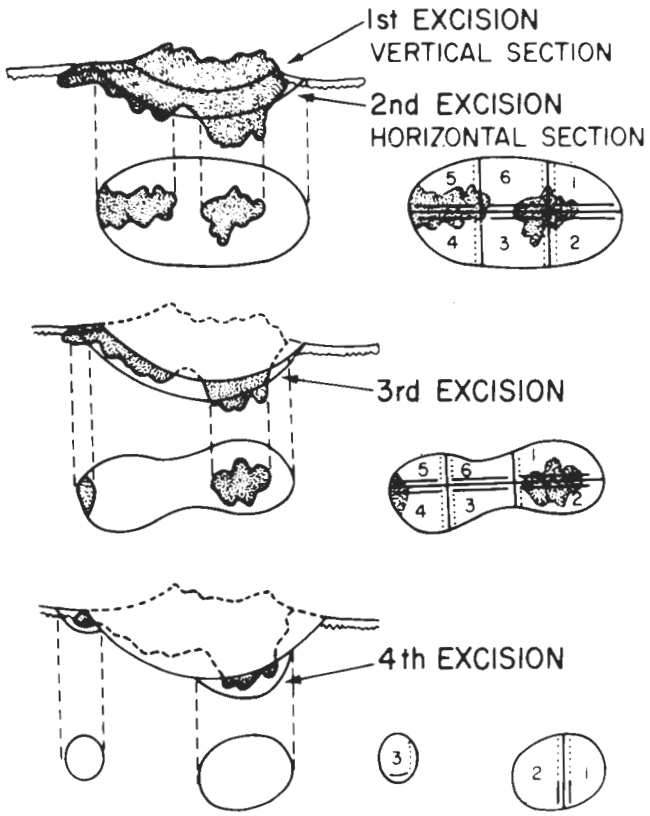

Figure 25-5. Successive excisions in fixed-tissue technique. (Helm F, Milgrom H, Rhelan JT, Klein E. Zur chemochirurgischen Behandlung der Hautkarzinome. Chemochirurgische Methode (nach Mohs) einer mikroskopisch kontrollierten Behandlung von Hautkrebsen. Dermatol Wochenschr 1964;44:453)

the clinically visible or palpable borders of the neoplasm. Involvement of the periosteum or nasal and orbital structures is not a contraindication. The procedure may be used for either basal cell or squamous cell carcinoma. Supporters of this technique report high success rates at 5 years. The major advantages, compared with other surgical methods, are the ability to precisely determine whether all of the tumor has been removed, and secondarily, to remove only as much normal tissue as is necessary, rather than guessing at the probable growth patterns.

The disadvantages of microscopically controlled excision include the multiple injections of a local anesthetic and the increased operative time of about 2 hours (with the fresh-tissue method). An experienced dermatopathologist must be available. Cosmetic and functional losses may be considerable, depending on the amount of tissue resected, the anatomic site affected, and whether healing is by secondary intention or reconstructive surgery. Examples of good cosmetic results after Mohs' surgery are shown in Figures 25-6 and 25-7.

CRYOTHERAPY. Cryotherapy produces excellent results for selected superficial basal cell carcinomas. A thermocouple is inserted into the base of the tumor to ensure a temperature of −30°C. A cryospray is used to freeze the lesion and a margin of normal tissue. The ice ball is allowed to thaw for 60 to 90 seconds and then the freezing is repeated. With properly selected lesions, the technique is successful with almost no risk of scarring, infection, or hemorrhage.

Liquid nitrogen may be applied topically to anesthetized lesions such as actinic keratosis, leukoplakia, carcinoma in situ, and multiple superficial basal cell carcinomas.

Radiation Therapy

The use of radiation therapy for treatment of skin cancer, although successful, has declined in recent years because of the greater availability of specialists to deal with the problems of skin cancer, the diminished use by dermatologists of radiation therapy in their private offices, and the late morbidity observed after short courses of radiation therapy given with a few high fractions. The radiation therapy skills available in the United States in the 1930s through the 1950s varied widely with correspondingly varied results. Radiation therapy, however, still plays an important role in specific anatomic situations in which the functional or cosmetic result is better than for a surgical modality, for large lesions that generally are not suitable for surgical treatment, and for patients medically unable to undergo an operative procedure. Much of the skin cancer irradiated in past years was treated with a few high-dose fractions, which often were successful in curing the cancer but eventually produced a depressed, unsightly scar, or worse. In addition, until recently, only orthovoltage radiation or implant techniques were available, so there was some constraint in treating large lesions involving cartilage or bone. With a wide range of energies, the constraints have largely disappeared, so that radiation therapy may be applied in almost any anatomic and clinical situation.

Chemotherapy

Some evidence exists that cisplatin-based chemotherapy produces gratifying responses, particularly when combined with surgery, irradiation, or both, in advanced squamous and basal cell carcinoma of the skin.[21] Also, adjuvant chemotherapy may be used in the management of Merkel cell carcinoma, using regimens similar to those employed in the treatment of small cell carcinoma of the lung. At this writing, however, no role has been proved for adjuvant chemotherapy in the treatment of skin carcinoma.

Selection of Treatment Modality

A comparison of the overall results of treatment of squamous cell carcinoma and basal cell carcinoma by radiation therapy and a variety of surgical techniques suggests that the cure rates are similar. Most comparisons are misleading, however, since lesions are not staged, nor are results given by anatomic site. The large number of small, successfully treated lesions tends to obscure the less favorable results seen in the larger, more aggressive tumors. Cure rates are uncommonly reported for greater than 5 years (eg, 10 to 15 years), and a significant number of cases recur late, which is in keeping with indolent nature of the majority of lesions.

Selection of treatment generally follows this priority list:

1. Cure
2. Function

Figure 25-6. (*A*) Recurrent basal cell carcinoma. (*B*) Surgical defect after Mohs' resection. (*C*) Reconstruction with a skin graft. (*D*) Cosmetic result at 6 months. (Courtesy of C. Stoer, MD, Gainesville, FL)

3. Cosmesis
4. Treatment time
5. Cost

The availability of specialists often determines treatment selection. The following factors are considered in treatment decisions:

- Anatomic location
- Size
- Invasion of contiguous structures
- Histologic features (particularly grade)
- Recurrent lesions
- Medical condition
- Mobility of patients

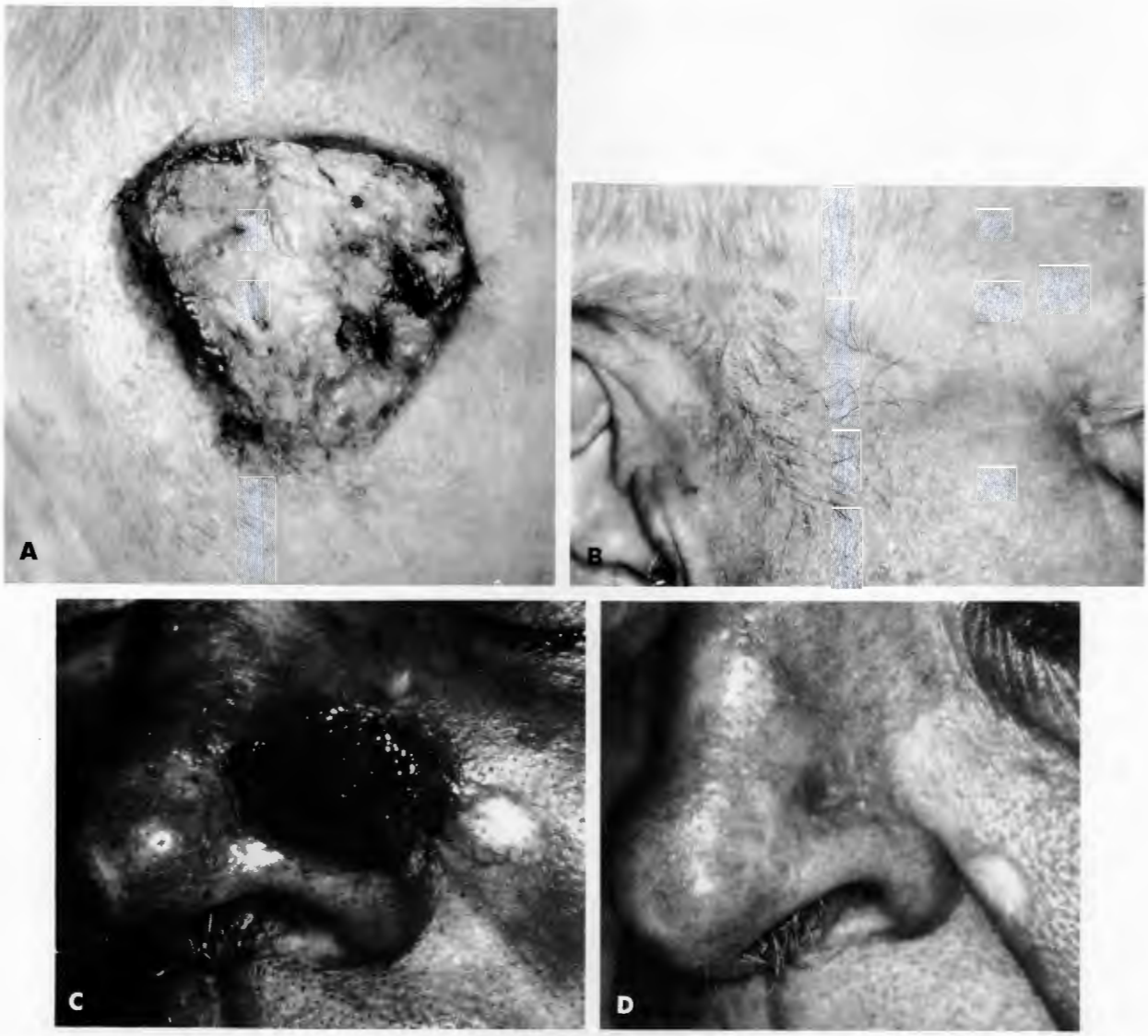

Figure 25-7. Examples of cosmetic result after Mohs' surgery with healing by secondary intention. (*A*) Surgical defect in right temple. (*B*) Cosmetic result. (*C*) Surgical defect in left nasal ala. (*D*) Cosmetic result. (*A* and *B* courtesy of F. F. Becker, MD, Vero Beach, FL; *C* and *D* courtesy of W. K. Stubbs, MD, Vero Beach, FL)

Both basal cell and squamous cell carcinomas are equally treatable by surgery or radiation therapy for similar-sized lesions; the histologic variants of basal cell carcinoma and squamous cell carcinoma, while perhaps suggesting a different prognosis and a minor adjustment in treatment technique, do not weigh heavily in the treatment decisions. Basal cell and squamous cell carcinomas are equally radiosensitive; the prescribed dose is based more on the size of the lesion, the extent of local invasion, and the contiguous normal tissues than on histologic features. The grade of the tumor, particularly a squamous cell carcinoma that is poorly differentiated, may influence treatment decisions in one direction or another. Recurrent lesions certainly require special planning, since their biologic makeup often is different from previously untreated lesions. A few of these recurrent lesions can never be controlled and, after many years of unsuccessful treatment, eventually cause major morbidity or the death of patients. Keratoacanthoma, while generally managed by a surgical modality, is reported to be as radiocurable as basal cell or squamous cell carcinoma.[9,51]

Favorable and Unfavorable Lesions

A favorable lesion is defined as a slow-growing lesion, with well-differentiated histologic features, discrete borders, and superficial penetration; not attached to contiguous structures or involving the ear, periorbita, or nose; and less than 2 to 3 cm in diameter. The vast majority of favorable skin lesions can be managed successfully with either scalpel excision, curettage and electrodesiccation, or cryotherapy. These treatments work well with little functional or cosmetic sequelae. Radiation therapy should be considered for favorable lesions if functional or cosmetic problems will result from the surgical procedure, or if complex and costly repair will be needed.

Unfavorable characteristics include a history of rapid

growth; poorly differentiated histologic type; infiltrative growth pattern (eg, sclerosing basal cell carcinoma); fixation to underlying structures; involvement of the ear, periorbita, cartilage, bone, or nerve; and recurrent lesions.

A 1- to 3-cm lesion can be easily excised in many locations with adequate borders, but in some areas the removal of 1 to 3 cm of tumor plus normal tissue implies functional and cosmetic loss, as well as an increased likelihood of cut-through. Primary closure often is not possible, and a graft or flap is required. For moderate-sized lesions, 1 to 3 cm, located in sites where excision may produce functional or cosmetic changes, radiation therapy must be considered. Radiation therapy often is selected for larger lesions (ie, more than 3 cm) that would require major resection and reconstruction, and for small lesions (1 to 2 cm) of the eyelids, canthus, pinna, tip and alar areas of the nose, and the skin of the upper lip. Multiple small lesions in one general area (eg, the nose) are better treated with radiation therapy (Fig. 25-8). Large recurrent lesions may require combined treatment with surgery and irradiation.

An often-repeated adage holds that lesions invading bone and cartilage should not be treated with radiation therapy. This simply is not true[39,40] (Fig. 25-9). The more advanced, neglected lesions invading cartilage or bone are, no doubt, more difficult to control by any means, but we have had modest success with radiation therapy for the treatment of lesions that involve bone and cartilage. We do not consider invasion of bone or cartilage a contraindication to the use of irradiation and, in fact, often prefer it. The use of supervoltage irradiation in these situations certainly has improved our ability to give larger doses to a larger treatment volume and still obtain healing. Numerous examples indicate cures by radiation therapy alone for lesions other than skin cancer that invade bone and cartilage (eg, squamous cell carcinomas of the gingiva, paranasal sinuses, nasopharynx, nasal vestibule, and larynx). When tumor invades bone and cartilage, if the bone or cartilage is expendable and the loss acceptable to patients, and if a good likelihood of obtaining adequate surgical margins exists, then surgical excision is selected. However, this set of circumstances is not often present with advanced lesions, and radiation therapy often is recommended as the sole modality, or in combination with resection. Cartilage invasion occurs to a minimal degree in association with relatively small lesions of the ear, nasal vestibule, or nasal skin; radiation therapy is not contraindicated in these cases, and the results are comparable with surgery. Adult cartilage has no blood vessels and a large amount of interstitial substance with only a few cells of low mitotic activity. High-dose, properly fractionated radiation therapy (6000 to 7500 cGy) incidentally delivered to normal adult cartilage (such as cartilage of the ears, larynx, nose, and ribs) almost never produces a chondronecrosis (see Chap. 13, section on cartilage necrosis). When adult cartilage is invaded by tumor, the occurrence of radiation-induced chondronecrosis still is unusual, even with substantial doses. Cartilage destroyed by tumor is replaced by connective tissue rather than by cartilage.[53] A diagnosis of chondronecrosis should be viewed with suspicion, since the more likely diagnosis is recurrent cancer.

Another adage often repeated in surgical texts is that large lesions might, in fact, be cured by irradiation, but patients would be left with a large, unhealed defect. Although this may happen, satisfactory healing by second intention does occur in most cases (Figs. 25-10 and 25-11). Healing of the large lesions is dependent on the redundancy and mobility of the adjacent tissues, as well as on the protraction of treatment over several weeks. However, in the case shown in Figure 25-12 of a huge, destructive scalp lesion, although the lesion disappeared after

Figure 25-8. (*A*) Multiple small superficial basal cell carcinomas of the nose and adjacent cheek with apparently normal intervening skin. (*B*) Appearance at 1 month.

Figure 25-9. (*A*) Squamous cell carcinoma invading the zygomatic arch, pinna, external auditory canal, temporal fossa, masseter, and parotid gland. Treatment plan was 6100 cGy over 5 weeks, cobalt-60, with wax bolus. (*B*) Appearance 1 month after treatment. (*C*) Appearance 2 months after treatment. (*D*) Appearance 6 months after treatment. Patient was alive with no evidence of disease at 6 years. (Courtesy of R. L. Lindberg, MD, Department of Radiation Therapy, M.D. Anderson Hospital and Tumor Institute, Houston)

radiation therapy, the epithelium could not cover the exposed bone and dura, and it was necessary to use local scalp flaps to cover the defect. We have successfully covered large defects with split-thickness skin grafts after therapy with 7500 cGy (see section on the scalp).

Perineural invasion, observed in less than 5% of patients who have carcinoma of the skin, is associated with a poor prognosis. This is particularly true in 30% to 40% of patients with pathologic evidence of perineural invasion who have signs or symptoms due to this phenomenon.[5,8,17,38] Perineural invasion is more often noted in squamous cell carcinoma than in basal cell carcinoma, and in recurrent as opposed to previously untreated cancer. Perineural invasion usually involves the second division of the fifth cranial nerve or the seventh cranial nerve. The first symptom may be the sensation of ants or worms crawling under the skin; if untreated, this progresses to pain, numbness, and motor deficits. Although perineural invasion usually grows toward the central nervous system, it may grow away from the central nervous system. The probability of local control at 5 years with irradiation alone in the University of Florida series is 20%.[38] The likelihood of local control was noted to improve to 40% with combined irradiation and surgery in a subset of nine patients; this did not, however, translate into an improvement in the 5-year survival rate (about 30% for both treatment groups).[38]

Selection of Treatment According to Anatomic Site

FREE SKIN. *Free skin* is a term used in some treatment centers to designate those areas of the cheek, temple, forehead, neck, and scalp that usually are not associated with potential functional or cosmetic loss if a lesion were surgically excised. Small to moderate-sized lesions in these areas are preferably treated by a surgical modality, since the approach is successful, quick and simple,

and less expensive compared with radiation therapy. Lesions that would require complicated and expensive reconstruction often are better treated with irradiation. Lesions that invade underlying bone, cartilage, or other adjacent structures (eg, the facial nerve) are treated by radiation therapy alone or in combination with an operation. It is difficult to obtain a deep surgical margin in many of these cases, and radiation therapy often produces a more acceptable functional and cosmetic result; excision may be reserved for radiation therapy failure.

NOSE. Four examples of nasal lesions before and after microscopically controlled excision of nonfixed tissues are shown in Figures 25-13 through 25-16.[44]

Nasal tip lesions tend to grow in a cephalocaudal direction and invade underlying cartilage (see Fig. 25-13)

Lesions of the columella invade the upper lip and premaxilla (see Fig. 25-14 and Chap. 22). The tooth roots may be invaded once tumor reaches the premaxilla.

Lesions arising on the lateral ala or the nasal labial crease tend to invade deeply ("iceberg" lesions) to involve the internal nose, inferior turbinate, and occasionally the nasolacrimal duct. Lateral spread occurs into the lip and cheek (see Figs. 25-15 and 25-16).

Recurrence is more often observed for nasal skin cancer than for any other site, whether treated with radiation therapy or with surgery.[30]

Nasal carcinomas often are more extensive than expected. The problems with acceptable nasal reconstruction dictate removal of as little normal tissue as possible. Unless these lesions are small and superficial, they are preferably treated with radiation therapy, which produces as good a local control rate as reconstruction and a better cosmetic result. Advanced lesions often are cured with radiation therapy, and although the cosmetic result is poor, it is usually more acceptable than total rhinectomy. Surgical excision, particularly of recurrent lesions, more often is successful using microscopically controlled excision.

(*text continues on page 660*)

Figure 25-10. (*A*) Squamous cell carcinoma of the right cheek. Note distinct borders. Treatment plan: 6500 cGy over 7 days, radium implant. (*B*) Partial healing at 3 months. (*C*) Complete healing at 1 year. No evidence of disease was seen at 5 years. Healing of defect was aided by redundant skin. (Courtesy of R. L. Lindberg, MD, Department of Radiation Therapy, M. D. Anderson Hospital and Tumor Institute, Houston)

Figure 25-11. Patient had a rapidly enlarging mass for 1 year. (*A*) A 12 × 16-cm squamous cell carcinoma was seen on the right cheek and temple with extension to the pinna. There was mild weakness of the frontal branch of the facial nerve and decreased sensation of the parietal scalp. Roentgenograms showed no bone destruction. Treatment plan: 6750-cGy tumor dose over 7 weeks, cobalt-60, with beeswax bolus, three fields. The neck received 5000 cGy over 5 weeks. (*B*) Fifty percent regression at 2500 cGy. (*C*) Completion of treatment. (*D*) Appearance at 6 months. No evidence of disease was seen at 5 years; the patient died of intercurrent disease at 5 years 10 months.

Figure 25-12. (*A*) Extensive (18 × 14 cm) basal cell carcinoma involving 60% of the scalp. The patient's presenting complaint was shortness of breath due to anemia (HbAg = 9.6 g). There was obvious bone destruction with tumor extending to dura in one area. (*B*) Lytic changes in parietal bone. Treatment plan was 2500 cGy (250 kV), then 4000 cGy over 6½ weeks cobalt-60 (^{60}Co). Bolus was added during the ^{60}Co therapy. (*C*) Appearance 2 months after radiation therapy. There was extensive exposure of necrotic bone; dura could be seen in one area. The bone was debrided and a scalp flap was used to cover the defect. A helmet with attached wig was fashioned for protection. (*D*) Appearance of patient without helmet at 5 years with no evidence of disease. She remains alive and disease-free 13½ years after irradiation.

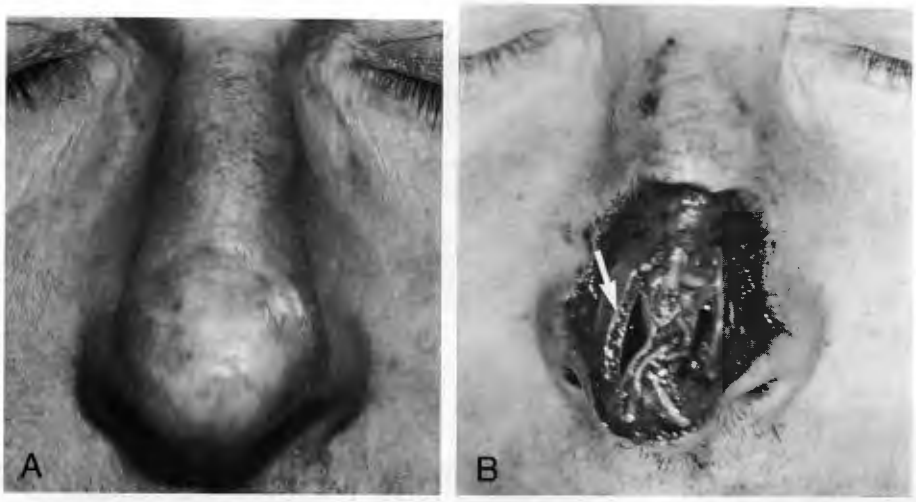

Figure 25-13. (*A*) Preoperative photograph of carcinoma of the nasal tip. (*B*) Microscopically controlled excision. It was necessary to remove part of the underlying cartilage to obtain satisfactory margins (*arrow*). This defect usually is repaired with a skin graft. (Panje WR, Ceilley RI. The influence of embryology of the midface on the spread of epithelial malignancies. Laryngoscope 1979;89:1916)

EYELIDS AND CANTHI. The inner canthus and lower lid are frequent sites of involvement for both basal cell carcinoma and squamous cell carcinoma.[16] Lesions arising in the medial canthus and root of the nose tend to invade deeply toward the medial orbit and lacrimal system and extend into the upper and lower lids. Lesions of the lateral canthus tend to invade the upper and lower lids, the lateral orbit, and the skin of the cheek and temple. Small lesions (1 to 5 mm) often can be treated by a surgical modality with a good functional and cosmetic result. The larger lesions, however, require excision of the underlying muscle (orbicularis oculi), the tarsal plate, or the lacrimal apparatus. Complicated repairs are required, the functional and cosmetic result may not be good, and the risk of local recurrence may be significant, even in experienced hands. Although the lids look acceptable in a photograph, varying degrees of functional loss occur once a flap is inserted. We prefer to treat most lesions that are greater than 5 mm and that involve the canthi and upper and lower lids with radiation therapy, assuming that patients are willing to undergo at least a 3- to 4-week treatment course. Short courses of radiation therapy produce satisfactory short-term results, but the late side effects may be undesirable, and the more prolonged fractionated treatments give lasting cosmetic and functional results that compete favorably with excision.

Extensive lesions of the periorbital area that grossly invade the orbit may require a combination of radical surgery and radiation therapy, including enucleation of the eye. However, radiation therapy alone will cure some of these advanced lesions (Figs. 25-17 and 25-18). A craniofacial procedure may be required to obtain clear margins in advanced lesions that invade the paranasal sinuses (see Chap. 22).

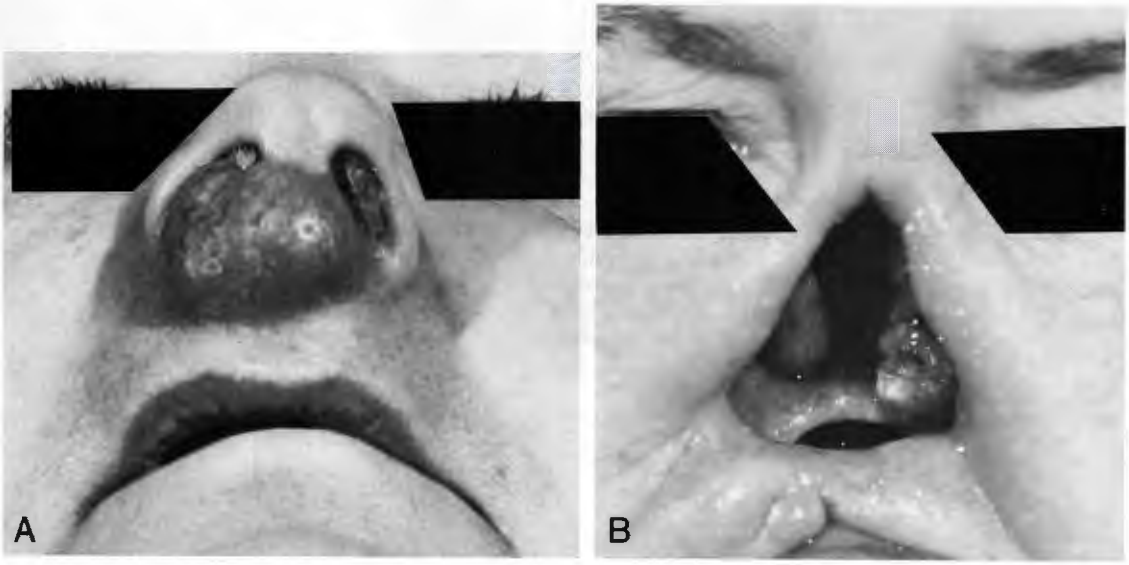

Figure 25-14. (*A*) Skin cancer of the columella. (*B*) Postoperative appearance. (Panje WR, Ceilley RI. The influence of embryology of the midface on the spread of epithelial malignancies. Laryngoscope 1979;89:1916)

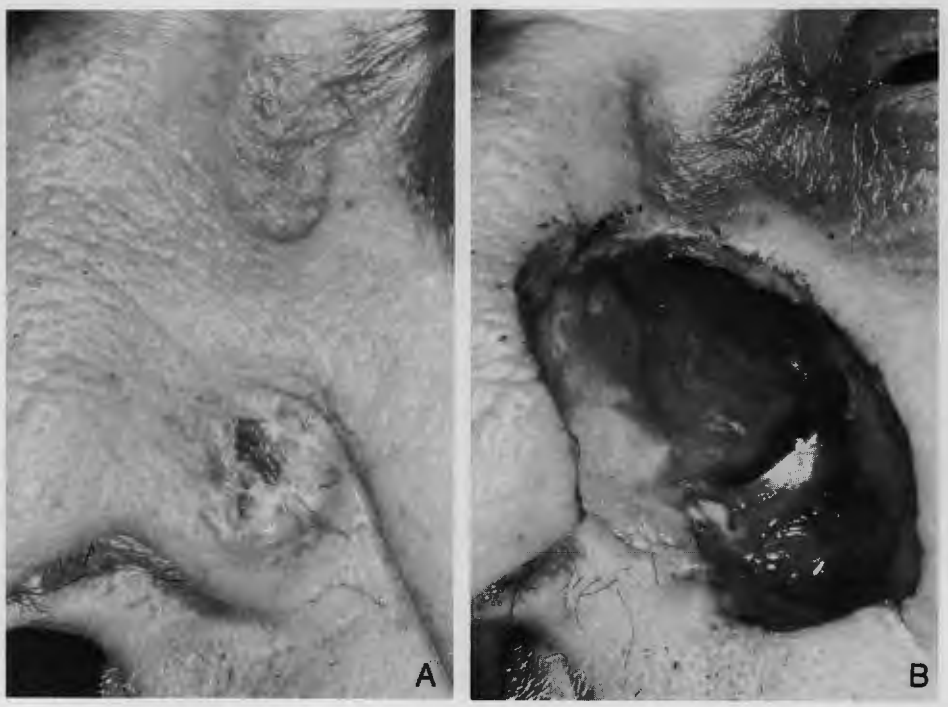

Figure 25-15. (*A*) Lateral alar basal cell carcinoma. (*B*) Appearance after excision. (Panje WR, Ceilley RI. The influence of embryology of the midface on the spread of epithelial malignancies. Laryngoscope 1979;89:1917)

EAR. Basal or squamous cell carcinomas occurring on the external ear may be treated by either excision or radiation therapy. Surgical procedures for small lesions may result in a minor cosmetic loss, but if this loss is relatively unimportant to patients, the results are satisfactory and the treatment is expeditious. Radiation therapy produces equal results without the cosmetic loss, but requires a longer treatment course. The often-stated fear of producing chondronecrosis with radiation therapy is unfounded if properly fractionated techniques are used.

Lesions in the concha frequently invade the external auditory canal and are less easy to cure by either surgery or radiation therapy. These lesions often have an infiltrative component that makes it difficult to define the extent of the lesion. If the cartilaginous canal is involved, then a sleeve resection or, occasionally, a temporal bone resection would be the surgical treatment (see Chap. 29). Radiation therapy also is used in these situations, probably with similar results.

SKIN OF THE UPPER LIP AND LIP COMMISSURE. Upper lip carcinomas tend to invade the lip vermilion, external nares, nasolabial crease, premaxilla, and lip commissure. Lesions less than 1 cm may be excised and closed primarily with an acceptable cosmetic

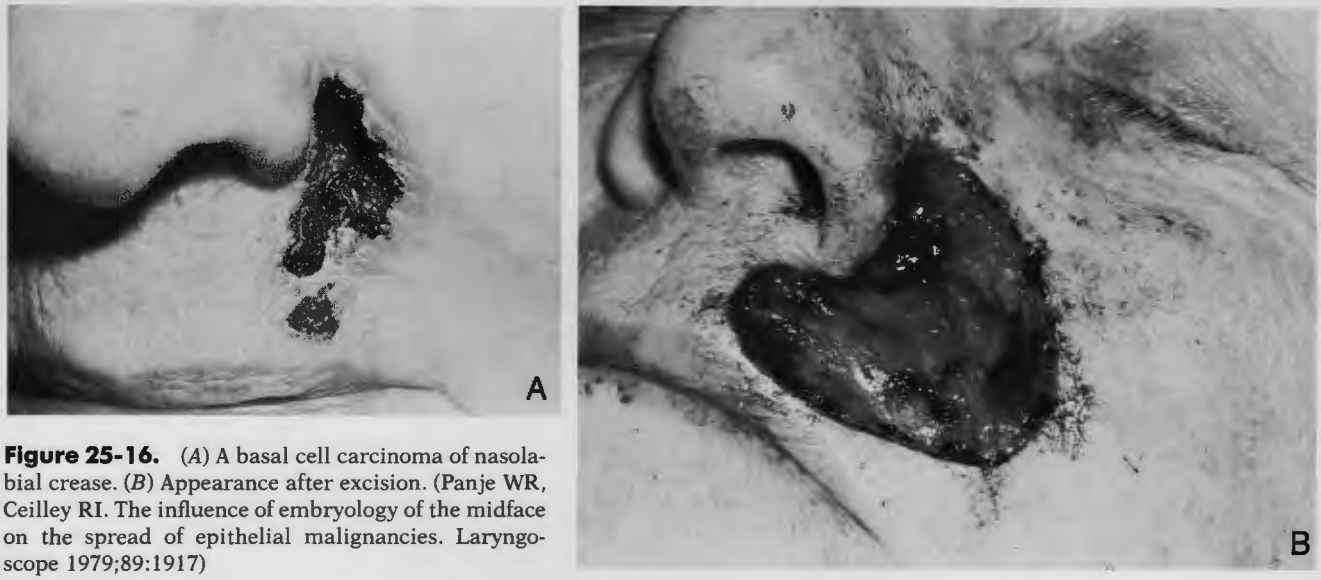

Figure 25-16. (*A*) A basal cell carcinoma of nasolabial crease. (*B*) Appearance after excision. (Panje WR, Ceilley RI. The influence of embryology of the midface on the spread of epithelial malignancies. Laryngoscope 1979;89:1917)

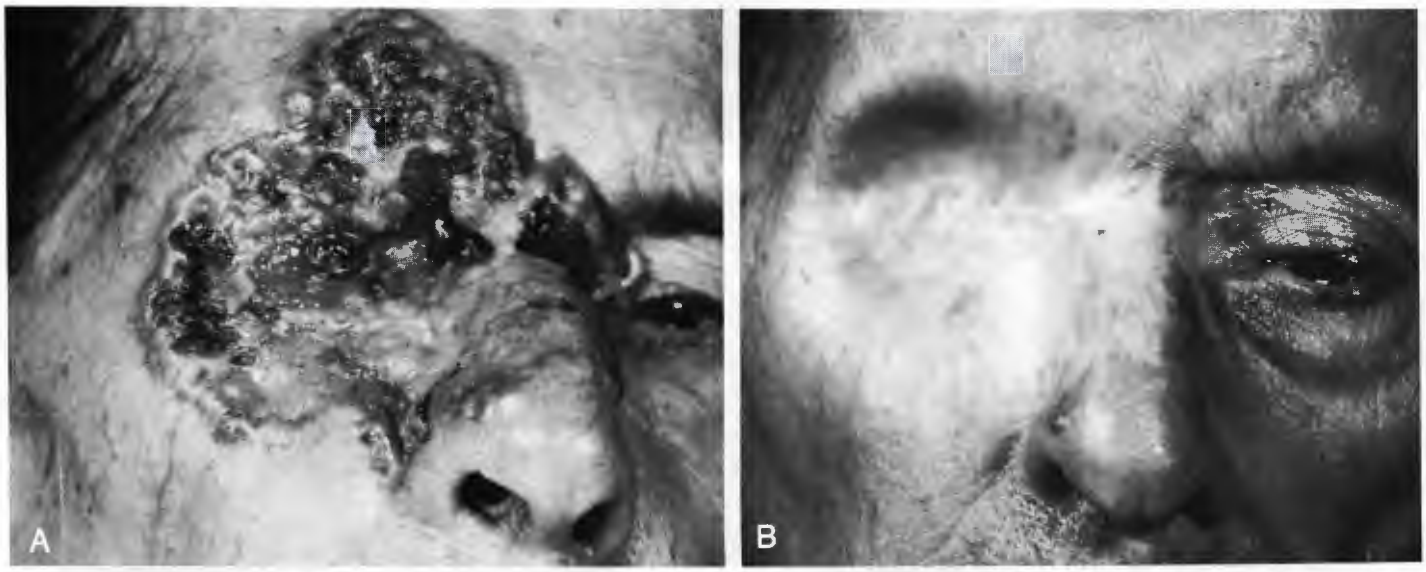

Figure 25-17. (*A*) Advanced basal cell carcinoma has destroyed the right eye, involves most of the nose, and approaches the left eye. (*B*) Appearance 3 years after orthovoltage therapy. (Courtesy of R. L. Lindberg, MD, Department of Radiation Therapy, M.D. Anderson Hospital and Tumor Institute, Houston)

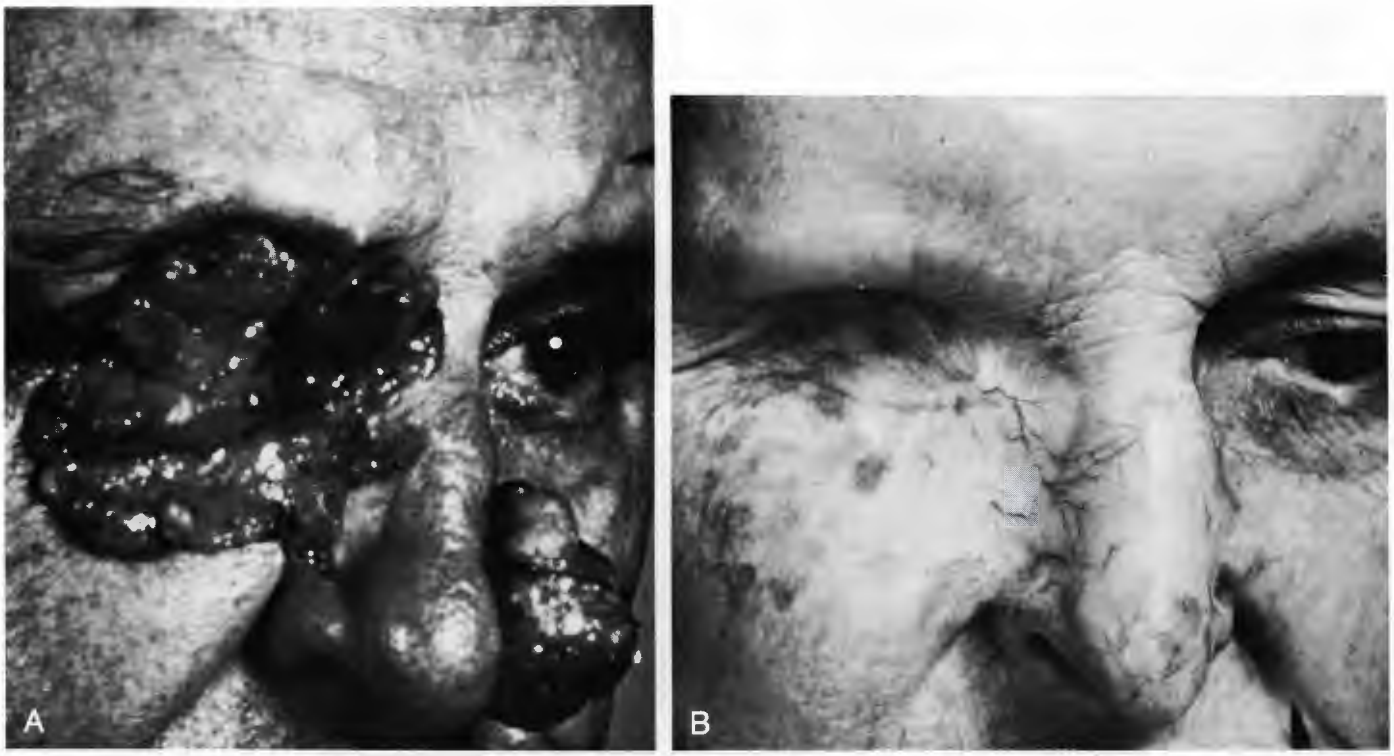

Figure 25-18. (*A*) Squamous cell carcinoma of the right medial canthus that has destroyed the right eye and lids; cystic basal cell carcinoma of the left nasal alar skin. (*B*) Appearance 5 years after orthovoltage irradiation. (Courtesy of R. L. Lindberg, MD, Department of Radiation Therapy, M.D. Anderson Hospital and Tumor Institute, Houston)

result. Lesions involving more than 1 cm of the skin of the upper lip may require excision of part of the nose, the lip vermilion, and the commissure and then may need complicated reconstruction; for this reason, we favor radiation therapy for the majority of these lesions (Fig. 25-19) (see Chap. 16, section on lip). Lesions involving the commissure are best treated with radiation therapy (Fig. 25-20).

ADVANCED LESIONS OF THE PREAURICULAR AREA AND CHEEK. The large, deeply infiltrative lesions in the cheek often invade cartilage and bone, the parotid gland, the facial nerve, and the infratemporal fossa, and they may be difficult to approach from a surgical standpoint. Radiation therapy often is recommended as the initial treatment. Examples of good results for these infrequent problems are shown in Figures 25-9 and 25-21.

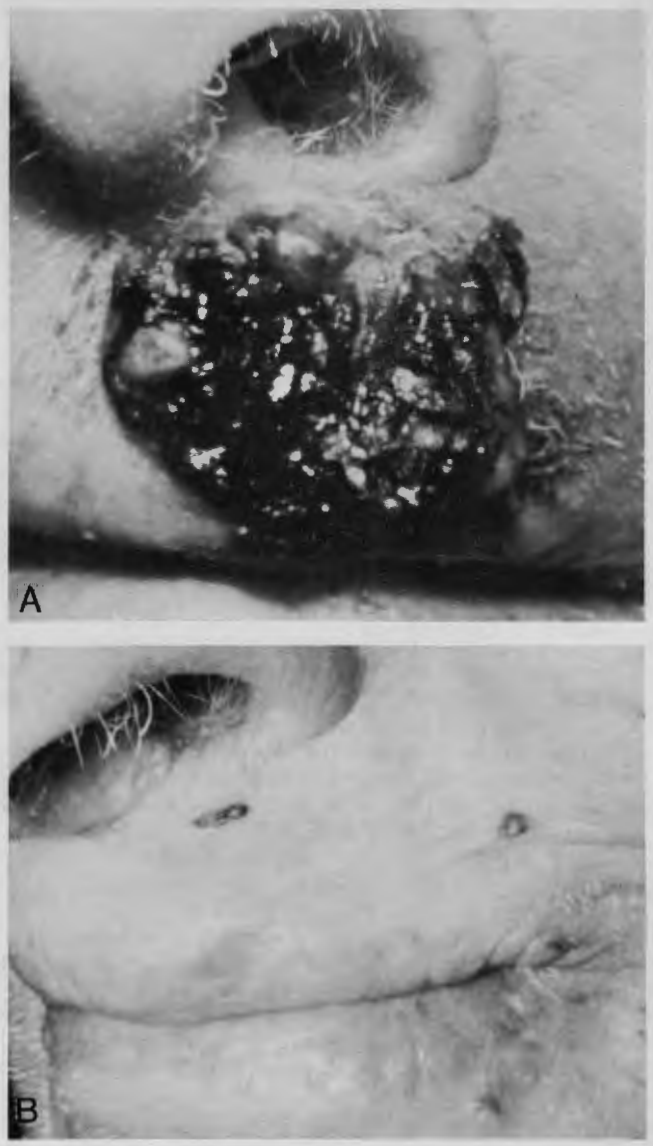

Figure 25-19. (*A*) A 3.0-cm basal cell carcinoma of the upper lip. (*B*) Appearance 7 months after treatment with a single-plane radium needle implant (7000 cGy at 0.5 cm). Patient died of intercurrent disease at 2 years.

SCALP. A preponderance of women is found in the small group of patients with large basal cell carcinomas of the scalp. These lesions appear at an earlier age than most skin cancer.[6] Small, superficial lesions of the scalp are best approached with surgical excision. Larger, deeply infiltrating lesions require removal of the subjacent periosteum or even some calvarium; invasion of dura and spread to regional lymph nodes occur in advanced lesions. Extensive lesions, either superficial or deeply invasive, may be treated with radiation therapy because of the large areas involved (see Fig. 25-12). Electrons may be of considerable advantage in these situations. Prior radiation therapy given for tinea capitis in childhood is a relative contraindication to a curative course of radiation therapy. Microscopically controlled excision also is successful for advanced lesions.[6]

Metastasis to Regional Lymph Nodes

The management of lymphatic metastasis is discussed in Chapter 6. However, metastases from skin cancer generally involve a different group of lymph nodes.

METASTASIS TO LYMPH NODES OF THE PAROTID AREA. Elective lymph node dissection in the parotid area generally is not recommended for squamous cell carcinoma of the skin, although some surgeons recommend it for malignant melanoma. If the primary lesion invades near or into the parotid gland, however, necessitating a parotidectomy, the lymph nodes should be removed at the same time.

If patients are at high risk for metastasis to the lymph nodes of the parotid area, but none is palpable, a reasonable alternative is elective irradiation to the parotid area and first-echelon neck lymph nodes.

When lymph nodes of the parotid area are clinically positive, the philosophy of management is similar to that for a high-grade parotid neoplasm. Lateral lobectomy, total parotidectomy, or radical parotidectomy is the initial procedure if the lesion is resectable, and the upper neck lymph nodes are removed. If lymph nodes are clinically negative in the upper neck, then an elective neck dissection is not done if postoperative radiation therapy is planned to the parotid bed, since the ipsilateral neck is electively irradiated in all cases. If lymph nodes are clinically positive, then a neck dissection is added to the parotidectomy. As in the management of high-grade primary parotid carcinomas, postoperative radiation therapy is recommended in nearly all cases.

Jackson and Ballantyne[26] reported an 84% control rate above the clavicles in a select group of 43 patients treated by surgery alone, and in whom the primary skin cancer was controlled. Postoperative or preoperative radiation therapy was added in 26 patients selected for a high risk of recurrence. The control rate above the clavicles was 88% (23 of 26). Radiation therapy was used for salvage of surgical failures in 12 cases, and 5 (42%) were successfully controlled. If postoperative radiation therapy is not planned, a more extensive operation, at least a total parotidectomy, may be needed to ensure a high control rate. We prefer to add irradiation in almost all cases rather than to increase the magnitude of the operative procedure.

If the parotid area metastasis is technically inoperable, then either preoperative irradiation or radiation therapy alone, including an interstitial implant, will cure a significant number of these patients (Fig. 25-22).

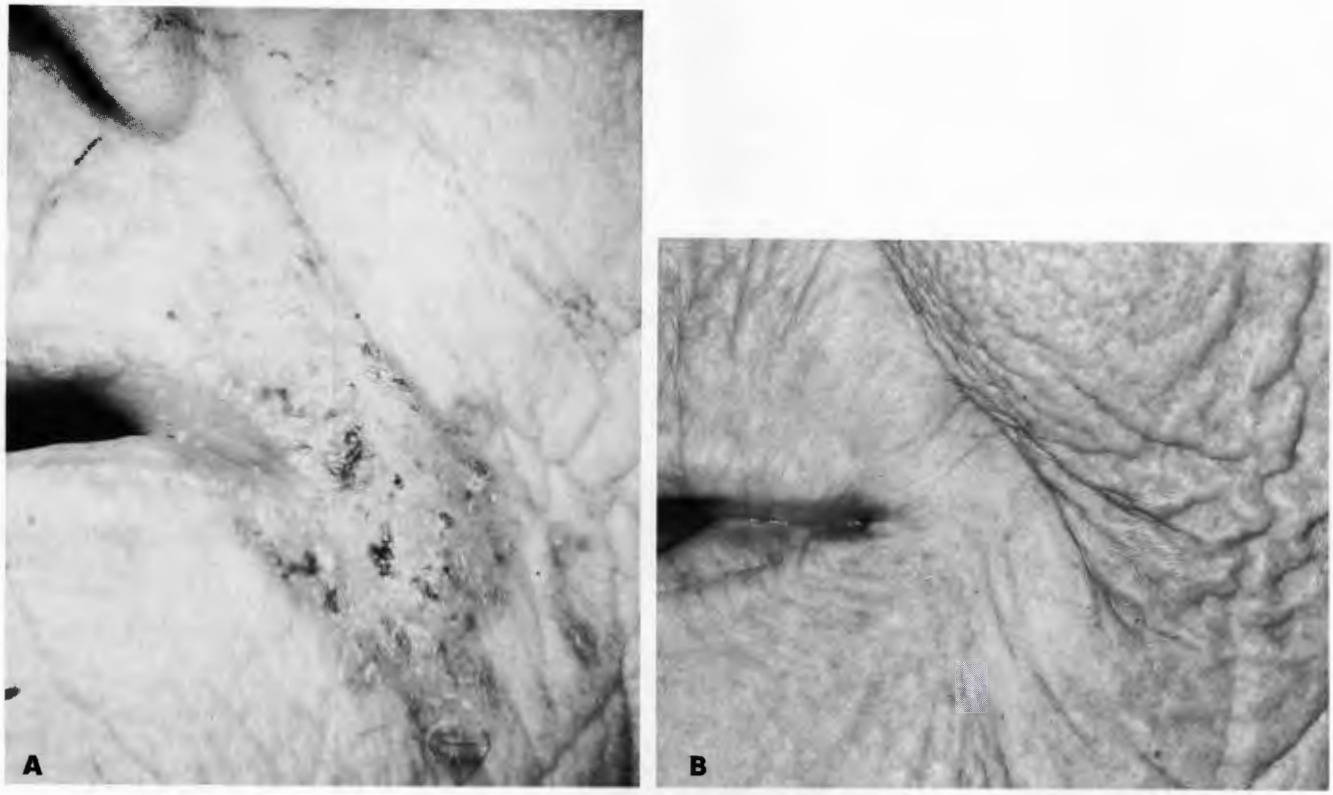

Figure 25-20. (*A*) Slowly enlarging superficial basal cell carcinoma of the cheek with involvement of the lip commissure. Treatment plan: 4750 cGy in 20 fractions over 6 weeks; 250 kV (split course). (*B*) There was no evidence of disease at 3 years.

Advanced preauricular metastases can produce a devastating situation since they may involve the tragus, a portion of the pinna, the external auditory canal, the facial nerve, the temporomandibular joint, the zygoma, the mandible, the temporal and infratemporal fossa, and the parapharyngeal space. Resection may produce a major functional and cosmetic loss, and therefore, radiation therapy alone may be considered to be a viable alternative to radical excision. External-beam irradiation combined with an interstitial implant is the usual treatment plan.

OCCIPITAL LYMPH NODE METASTASES. The regional metastases are removed by a posterolateral neck dissection; a supraomohyoid or standard neck dissection is added according to the situation (see Chap. 6, section on neck dissection).

POSTAURICULAR AND MASTOID LYMPH NODE METASTASES. A regional lymph node dissection is done, and a supraomohyoid or standard neck dissection is added.

Adnexal Carcinomas

Surgical excision is the usual recommendation for the adnexal carcinomas. We have limited experience with radiation therapy for these neoplasms, and most of the experience is for postoperative radiation therapy or unfavorable recurrent lesions. Gross lesions do respond to radiation therapy, however, and a few of favorable size are probably cured (Fig. 25-23).

(*text continues on page 669*)

Figure 25-21. A 59-year-old woman had an 18-month history of an enlarging lesion on the right temple. There was decreased hearing and pain in the temporomandibular joint when chewing. An 11- by 10-cm lesion of the right preauricular area extended to within 2 cm of the lateral canthus. The pinna was obviously destroyed, and the external auditory canal was filled with tumor. Paralysis of the orbital branch of the facial nerve was noted. Biopsy revealed basal cell carcinoma. Tomograms showed early erosion of the posterior zygoma, temporamandibular joint, and mastoid process. Treatment plan: ipsilateral cobalt-60 portal with a 5-mm layer of petrolatum gauze for bolus; 7000 cGy at 0.5 cm over 7 weeks. (*A*) Appearance before therapy. (*B*) Appearance after 2400 cGy. (*C*) Appearance at end of treatment. (*D*) At 6 months there was 80% healing of the tumor bed; complete healing was evident at 8 months. The patient developed radiation caries. (*E*) Appearance at 3½ years. (*F*) At 3½ years, paralysis of the ophthalmic branch of facial nerve persisted. The patient had no evidence of disease at 12½ years. ►

Figure 25-21.

Figure 25-22. (*A*) Squamous cell carcinoma metastatic to parotid lymph node. Squamous cell carcinoma of skin of temple treated 2 years before admission (*arrow*). Note that tragus is minimally involved, even when the parotid lymph node is involved, the tragus and pinna are involved early in the course. (*B*) Modified three-plane radium needle implant. One plane (four needles) is placed in the retromandibular deep lobe. (*C*) Lesion was completely healed at 1 year (no evidence of disease at 9 years). (Courtesy of R. L. Lindberg, MD, Department of Radiation Therapy, M.D. Anderson Hospital and Tumor Institute, Houston)

Figure 25-23. A 69-year-old man had a slowly enlarging, asymptomatic growth on the right side of his nose beginning 10 years before admission. He underwent a reduction for rhinophyma 2½ years before admission. Microscopic diagnosis was sebaceous hyperplasia with rhinophyma. Shortly after the operation, the nodularity reappeared and has grown slowly. He underwent repeat operations for rhinophyma, and the tissue contained sebaceous carcinoma. (*A*) Appearance 1 month after surgery. There was a firm, white, slightly elevated scar overlying a 5 × 4 cm palpable mass of the right side of the nose and premaxilla with fullness in the nasolabial crease. (*B*) Tumor in lateral nasal vestibule. The mass extended approximately 3 cm into the nasal cavity. The patient refused operation and received 5000 cGy over 5 weeks, cobalt-60 (with bolus). There was 60% to 70% tumor regression. (*C*) Iridium implant. The dose was 3200 cGy. (*D* and *E*) Appearance at 3 months. Patient was free of disease at 12 years. (Courtesy of T. Bloom, MD, and H. Kerman, MD, Department of Radiation Therapy, Halifax Hospital, Daytona Beach, FL)

Figure 25-23.

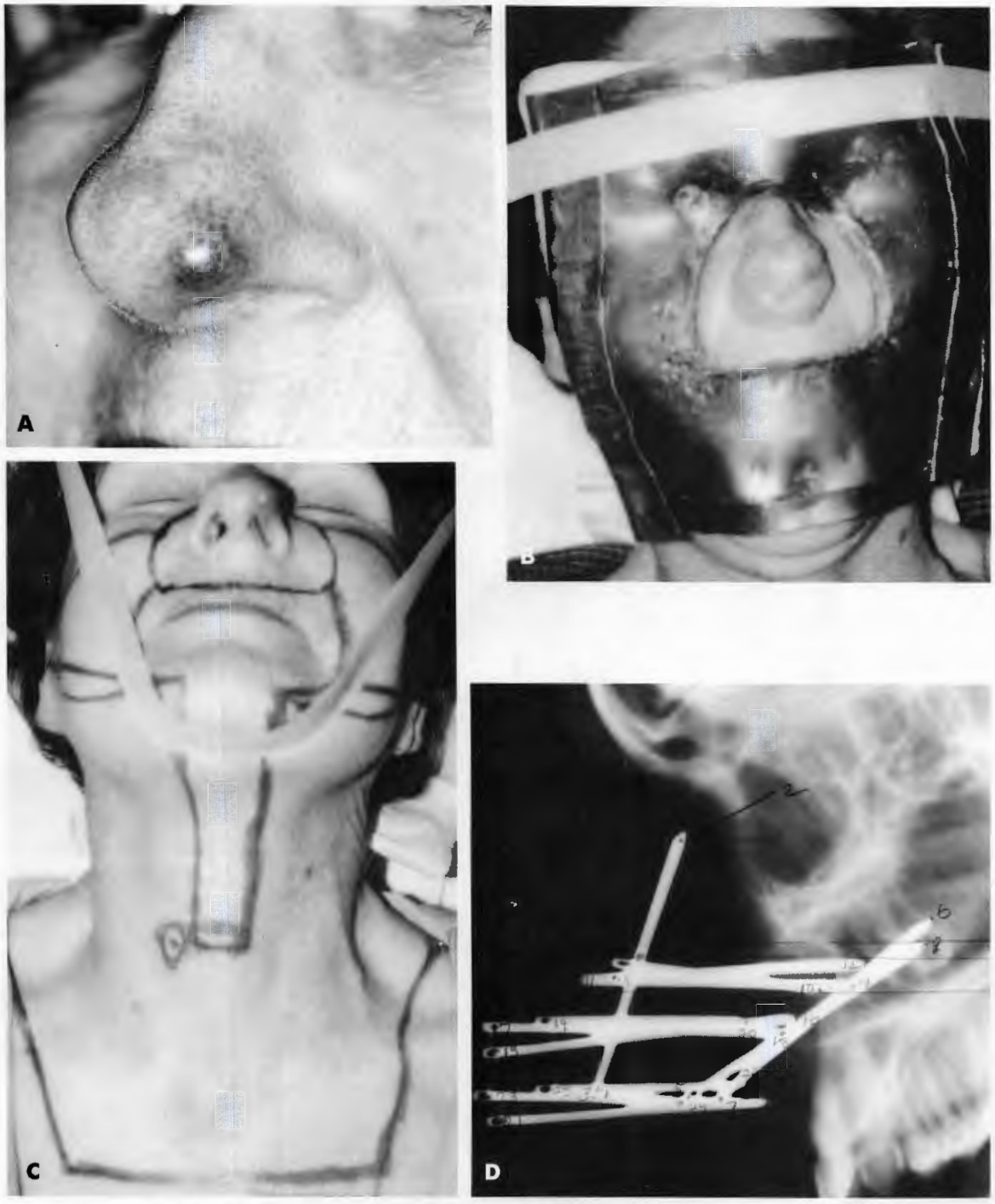

Figure 25-24. A 69-year-old woman with T1N0 Merkel cell carcinoma involving the tip of the nose and left nasal vestibule treated with irradiation alone. (*A*) Before treatment. (*B*) 5000 cGy in 25 fractions with 20-MeV electrons to nose. A lead mask was used to collimate the beam on the skin surface. Beeswax bolus was placed into the nares bilaterally and covering the nose (not shown) to provide a homogeneous dose distribution. (*C*) The intercalated facial nodes were electively treated with 10 MV electrons to 5000 cGy in 25 fractions at maximum dose (Dmax); the neck received 4050 cGy in 15 fractions at Dmax with 8-MV x-ray. (*D*) A three-plane radium needle implant was used to boost the primary lesion 1750 cGy over 35 hours. (*E*) The patient is disease–free at 1 year after treatment.

Figure 25-24. (*Continued*)

Merkel Cell Carcinoma

Resection of the primary tumor and any regional lymph nodes believed to be involved is the treatment of choice for Merkel cell carcinoma. Postoperative irradiation may be indicated depending on pathologic parameters such as close margins, perineural invasion, and lymph nodes with positive findings.[43] If excision of the primary lesion would result in unacceptable cosmesis, irradiation alone is a reasonable alternative (Fig. 25-24). If clinically negative, the regional lymphatics should be managed electively with surgery or radiation therapy at the time that the primary lesion is treated. The role of adjuvant chemotherapy in the management of Merkel cell carcinoma is unclear. Theoretically, adjuvant chemotherapy, using drugs employed to treat small cell lung carcinoma, should decrease the relatively high incidence of distant metastases and improve the likelihood of cure for Merkel cell carcinoma. No solid evidence exists, however, that this is the case. Therefore, adjuvant chemotherapy for Merkel cell carcinoma should be regarded as investigational.

Surgical Excision

This section deals primarily with scalpel excision. Curettage and electrodesiccation, cryotherapy, fulguration, and microscopically controlled excision produce good results when applied to suitable lesions. An in-depth discussion of the technical aspects of these treatments is beyond the scope of this chapter, however.

A margin of about 5 mm beyond the edge of the lesion is sufficient for small, discrete tumors; proportionately more is required for larger lesions. The most common site to cut across the tumor is not at the lateral edge but at the deep aspect, and this portion of the specimen should be checked by frozen section if any question exists about the adequacy of the resection. Lesions on the mobile skin are excised using an ellipse with a 4:1 ratio of length to width; the skin is mobilized and closed primarily. Lesions excised from an area of fixed skin such as the tip of the nose, or large lesions, may require either a split-thickness skin graft or a local flap closure. When resecting large or recurrent lesions, covering the area with thick flaps is not preferred, since this makes it difficult to observe for recurrence. In some cases, using a prosthetic device is preferable for the initial rehabilitation (eg, after rhinectomy), allowing observation for 2 to 3 years before attempting reconstruction, unless the patient demands immediate repair.

Significance of Positive Margins After Excision

Occasionally, a lesion is excised and the pathology report states that tumor is present close to the margins, or that the margins are positive. The alternatives are reexcision, irradiation of the tumor bed, and observation. Although not all cases with positive margins recur,[19] recurrent lesions cannot all be cured.

An individualized decision is made in each case when close or positive margins exist. One must weigh the factors of the anatomic site, patient age, the histologic type, the previous therapy, and history of the growth pattern to reach a decision to recommend additional treatment or to observe patients. For instance, the finding of a positive margin after excision of a basal cell carcinoma of the inner canthus or nasolabial fold is a potentially serious problem, since the recurrence may be difficult to detect and salvage might require major therapy. On the other hand, a small basal cell carcinoma excised from a free skin area with a close or positive margin might be safe with observation only, since recurrence is more easily diagnosed and treated. A small squamous cell carcinoma from a free skin site with a positive margin would dictate additional therapy, however, since the threat of lymph node metastasis, albeit low, would be an additional consideration.

Reexcision may be used in areas where ample tissue is available to reexcise without producing a functional or cosmetic problem. Most cases with positive margins, however, occur either in patients with large lesions who have already had a flap reconstruction, or in areas where resection of additional tissues may not be desirable.

Another difficulty with immediate reexcision is that usually a localized inflammatory reaction occurs around the old surgical site, and since a minimal amount of tumor typically is present, the pathologist may not be able to assist the surgeon with margin checks. Radiation therapy has the advantage of being able to cover a fairly wide area, and this modality often is selected for patients with positive margins.

Surgical Treatment According to Anatomic Site

SCALP. Small lesions can be excised with primary closure. Large lesions require full-thickness resection with, perhaps, a cuff of periosteum, or even the outer table of the calvarium. A split-thickness skin graft or flap is required for coverage. A split-thickness skin graft can be applied over the bare skull and usually will take if the cortical bone is drilled down to bleeding bone. A scalp flap, posterior cervical flap, forehead flap, or free flap may be rotated to cover the defect. If the full thickness of the skull is removed, a protective helmet may be required.

FOREHEAD. Most lesions of the forehead may be excised with a primary closure along the natural skin lines. Larger lesions may require a split-thickness skin graft or local flap. Advanced lesions may invade the periosteum and require removal of adjacent bone[44] (Fig. 25-25).

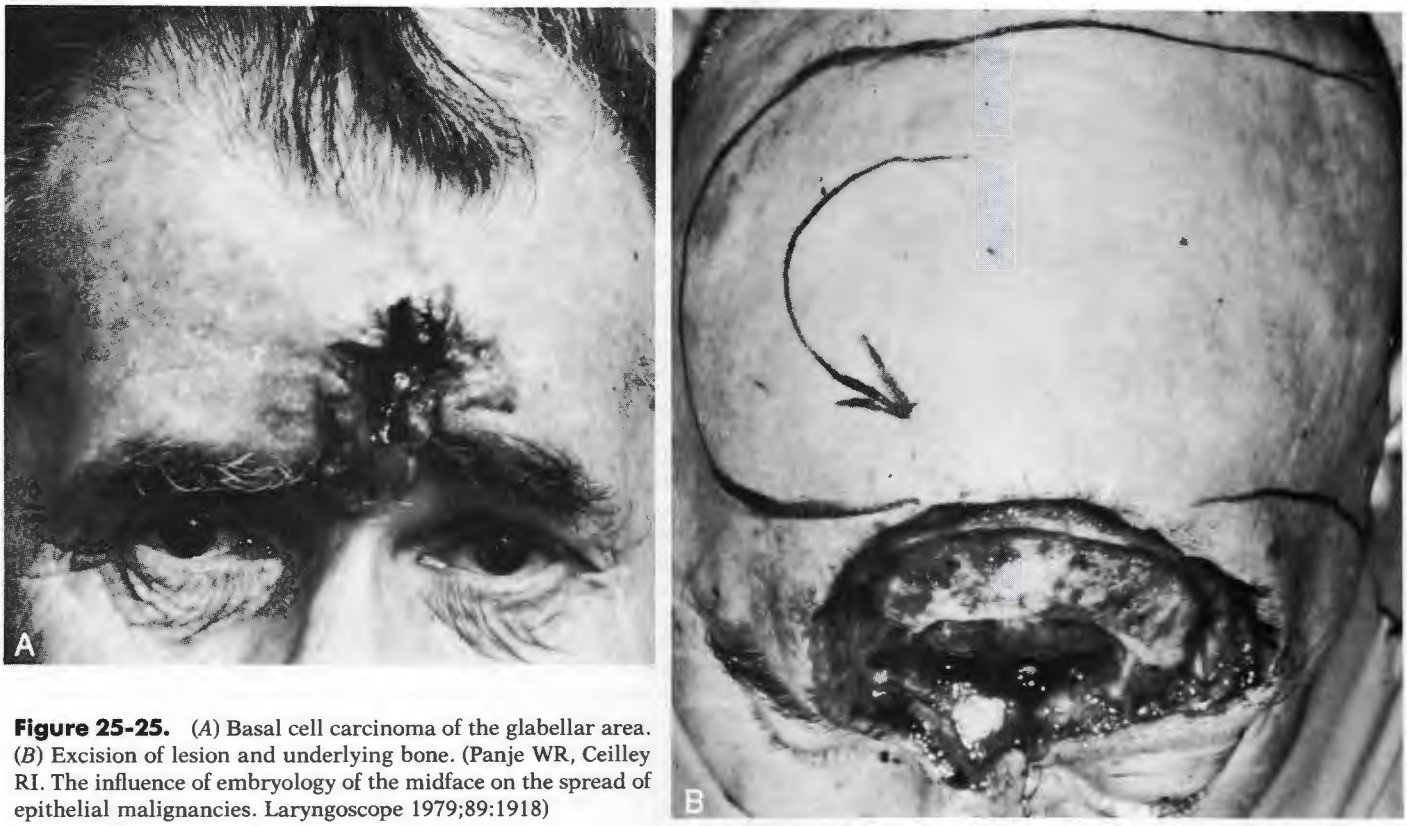

Figure 25-25. (*A*) Basal cell carcinoma of the glabellar area. (*B*) Excision of lesion and underlying bone. (Panje WR, Ceilley RI. The influence of embryology of the midface on the spread of epithelial malignancies. Laryngoscope 1979;89:1918)

EAR. Small, superficial lesions not invading cartilage can be excised with a cuff of perichondrium or cartilage. The skin is fixed to the underlying perichondrium, so other means of closure must be used. Through-and-through V-excisions from the helix may be repaired with primary closure.

A retroauricular pedicle flap may be used to reconstruct small defects. Large lesions require total or near-total removal of the external ear, often in connection with partial temporal bone resection; a prosthesis is required to reconstruct the external ear. It is advantageous to leave a small amount of the superior portion of the ear intact to help attach the prosthesis and to facilitate the wearing of glasses. Osteointegrated implants are available to attach the prosthesis; prior irradiation of the area containing the implanted device is a contraindication of this reconstruction technique.

PERIORBITAL AREAS. Small lesions, 5 mm or less, on the eyelid may be excised and closed primarily without noticeable cosmetic or functional changes. Larger lesions that involve the edge of the eyelid are resected and repaired by either a rotation flap or a graft from the upper eyelid. Resection of one third or more of the lid requires a more complex reconstruction. The lid may be reconstructed and have an acceptable appearance, but it has little functional activity, and the cosmetic appearance is not as good as it appears in a still photograph. About one fourth of the upper lid can be excised and directly approximated with acceptable results. Excision of greater portions of the upper lid requires a full-thickness pedicle flap. Large or recurrent lesions that invade the periorbital fat or muscles of the eyeball require an orbital evisceration or exenteration. This defect usually is repaired with a split-thickness skin graft; postoperative irradiation is frequently advised.

NOSE. Small lesions on the bridge of the nose may be simply excised with primary closure, but larger lesions require a split-thickness skin graft or full-thickness rotation graft for coverage. Superficial lesions around the nasal alar areas or the tip of the nose are resected down to the perichondrium of the cartilages. The skin is immobile over these cartilages and must be repaired by a local flap or split-thickness graft. Lesions that are tethered to the cartilages require removal of underlying cartilage to obtain a tumor-free margin. These defects usually are repaired with a composite graft. The more deeply infiltrative lesions may extend through the crevices between cartilages and invade the submucosa of the nasal cavity. Microscopically controlled excision is desirable for these cases to avoid positive margins or excessive resection of normal tissue. Radiation therapy is preferable because of better cosmetic results. Large lesions, or recurrent lesions after irradiation, require partial or total nasal resection. These defects may be repaired either with a nasal prosthesis or by reconstruction with a forehead or tube-pedicle flap, with or without an autologous bone graft.

Lymph Node Metastases

Operations for removal of lymph nodes of the parotid area are highly individualized because of the anatomy of the region and the close association of the lymphatic tissue with the facial nerve.

Contrast-enhanced CT is recommended pretreatment to assist in the planning of a surgical procedure in patients with clinically involved lymph nodes of the parotid area, particularly regarding extension to the deep lobe of the gland and toward the parapharyngeal space.

Graham[20] studied the distribution of the parotid lymph nodes in cadavers by serially sectioning either the entire parotid gland or the residual gland after a superficial parotidectomy in the plane of the facial nerve. Study of the whole gland showed that the lymphatic tissue lay lateral to a plane passing through the main vascular bundle within the gland, and that removal of that portion of the parotid lateral to the vascular bundle was effective in removing parotid lymphatic tissue; dissection along the facial nerve would leave a substantial amount of lymphatic tissue, in most instances.

In an elective parotid lymph node dissection, a lateral parotidectomy in the vascular plane, rather than the facial nerve plane, should encompass all of the lymphatic tissue; however, the risk of damage to the facial nerve precludes parotidectomy in this plane.

If clinically palpable nodes are present at the time of the resection of the primary lesion, the primary lesion may be excised separately or through a single incision, as shown in Figure 25-26. In the majority of cases, however, metastases to the lymph nodes of the parotid area appear at some point after successful treatment of the primary lesion. If the lymph nodes are small and mobile, then a lateral lobectomy in the plane of the nerve, in combination with an upper neck dissection, is the treatment of choice. If the lymph nodes are large and tumor is growing through the capsule of the lymph nodes with fixation to skin, extension to the tragus or pinna, or gross invasion of the facial nerve, masseter muscle, mandible, or deep lobe of the parotid gland, then an individualized major resection of the parotid and involved tissues is required. One should not rely on high-dose postoperative radiation therapy to sterilize the gross residual disease, and every attempt should be made to obtain a tumor-free margin. Preoperative irradiation should be considered in the advanced cases.

If lymph nodes in the neck have positive clinical or pathologic findings, then an appropriate neck dissection is added to dissection of the lymph nodes of the parotid area. If lymph nodes of the upper neck give pathologically negative results, no further neck dissection is done, and the entire ipsilateral neck is included in the postoperative irradiation plan.

For a discussion of posterolateral neck dissection, see Chapter 6, section on neck dissection.

Irradiation Technique

With the increased availability of specialists dealing with treatment of skin cancer by surgical modalities, the routine use of radiation therapy has greatly diminished during the last three decades. Dermatologists generally have stopped giving radiation therapy in their offices in recent years, which further reduced its use as a treatment option.

The contraindications are prior high-dose irradiation within the area of the skin cancer, skin cancer developing on the site of a burn or chronic infection, and lesions of the palms and soles of the extremities. Relative contrain-

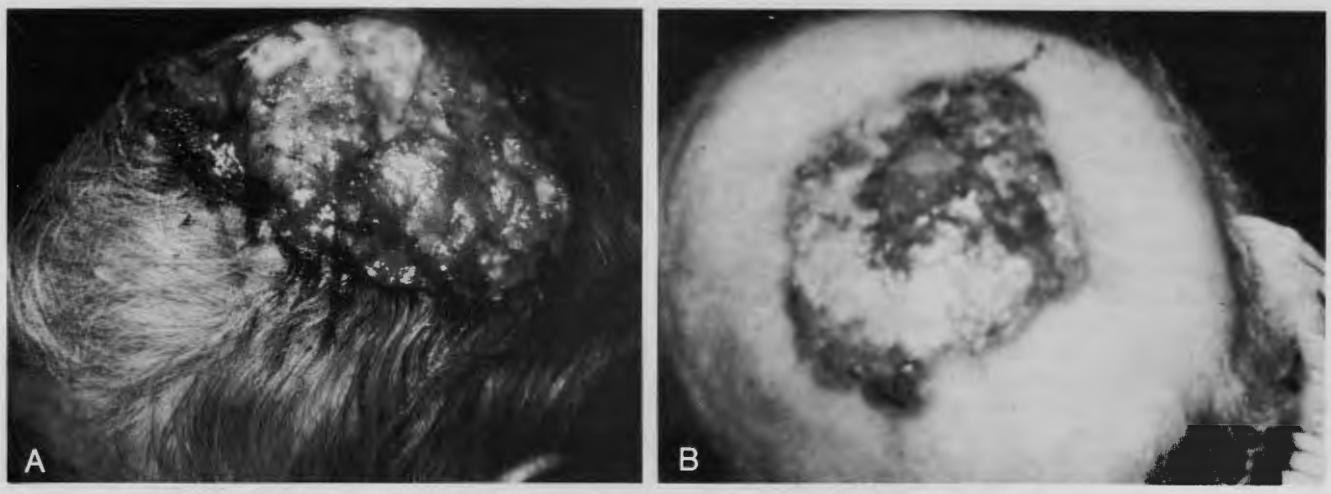

Figure 25-26. A 55-year-old man had a 6-year history of a dime-sized flat sore on the left temple and a 2- to 3-year history of a small subcutaneous lump in left preauricular area. He received a course of topical 5-fluorouracil to the temple lesion without a biopsy. The lesion suddenly began to grow after 6 weeks of treatment. (*A*) Elevated, red lesion on temple was 2.5 × 2 cm. There was a 2- × 1-cm, mobile left parotid area lymph node. The recommendation was excision of primary lesion, parotidectomy, and postoperative radiation therapy. Pathologic findings were squamous cell carcinoma of skin with margins free and one positive parotid lymph node. (The gross appearance of the primary lesion was consistent with nodular melanoma.) (*B*) Appearance 6 weeks after surgery. The patient received postoperative radiation therapy to the tumor bed and left neck. The primary site and parotid bed received 6500 cGy over 7 weeks, mixed beam, 17-MV x-ray and 20-MeV electrons. The left lower neck received 5000 cGy over 5 weeks. Radiation therapy was recommended despite negative margins in view of the history of rapid growth, narrow margins, and small possibility of occult disease in the neck. No evidence of disease was found at 6 years.

dications include use in young patients, especially those with complexions likely to develop multiple skin cancers, prior use of low-dose irradiation (as in the treatment of acne), xeroderma pigmentosum, and discoid lupus. Involvement of bone or cartilage is not a contraindication, contrary to what is written in most surgical texts.[40] Numerous examples exist of cures by radiation therapy alone with bone or cartilage involvement. In fact, for large-sized skin cancer, we find little difference in cure rate whether or not these tissues are involved. The cure rates for advanced primary carcinomas of the nasal cavity, paranasal sinuses, nasopharynx, gingiva, and larynx with evidence of bone or cartilage invasion certainly are significant, and no difference should be expected with skin carcinoma. When tumor invades bone or cartilage, the treatment decision hinges more on whether the involved structure is expendable. For example, a portion of the ramus of the mandible or a portion of the maxilla might be resected with limited functional and cosmetic loss. Resection of the lesions shown in Figures 25-9 and 25-21, however, would produce a major cosmetic defect with a low chance of obtaining adequate margins, and radiation therapy, therefore, is preferred. In fact, one of the indications for radiation therapy is an advanced lesion invading bone or cartilage.

Radiation therapy is most commonly indicated for small lesions around the nose, eye, ear, upper lip, and commissure of the lip; for advanced lesions invading bone or cartilage; after an incomplete excision; for advanced lesions in general; for patients at poor medical risk for a surgical procedure; for multiple adjacent small lesions (eg, on the nose); and for metastatic spread to regional lymph nodes.

A wide range of techniques is available for the treatment of skin cancer, including orthovoltage and supervoltage x-rays, electrons, and interstitial techniques. The selection of technique is highly individualized and depends on the tumor volume, normal tissues to be protected, available equipment, the experience of the radiation therapist, and patient mobility. Orthovoltage irradiation is associated with a higher probability of local control compared with electron-beam irradiation.[31]

Guidelines for selection of the external-beam dose, based on the size of the lesion, the functional or cosmetic result desired, and patient age and mobility, are given in Table 25-1. Short treatment schemes of one to five treatments are curative for small or medium-sized lesions, but eventually a depressed scar or other complications may result. The late effects of these short schemes have given radiation therapy a bad name in the management of skin cancer, and rightly so, since it usually falls on the surgeon to manage the late complications. These short treatments are particularly undesirable around the eye, nose, and ear. The short regimens are mostly used for the immobile, elderly patient who is able to make only a few visits to the radiation therapy department.

TABLE 25-1. Guidelines for Selection of External-Beam Dose

Orthovoltage Dose (cGy)*	Examples
6500 cGy/7 wk	Large untreated lesion with bone or cartilage invasion, or large recurrent tumor†
6000 cGy/7 wk	Large untreated lesion with minimal or suspected bone or cartilage invasion†
5500 cGy/6 wk	Moderate to large inner canthus, eyelid, nasol, or pinna lesions (20–30 cm^2 area)
5000 cGy/4 wk	Small, thin lesion (<1.5 cm) around eye, nose, or ear (10 cm^2 area)
4500 cGy/3 wk	Moderate-sized lesion of free skin or postoperative cut-through of moderate size on free skin‡
4000 cGy/2 wk or 3000 cGy/1 wk	Small lesions (1 cm) on free skin‡
The following schemes are used when the late cosmetic result is not important and travel for the patient is difficult:	
4000 cGy/10 fractions or 3000 cGy/5 fractions or 2000/1 fraction	Rapid fractionation schemes produce a high cure rate for small lesions, but the cosmetic result may be less than optimal after 5 y

* Add 10% to dose for supervoltage therapy.
† All, or a portion, of the therapy given with supervoltage photons or electrons.
‡ *Free* indicates no involvement of ear, nose, eye, or lid.

Irradiation Techniques According to Anatomic Site

EYELID. Almost all early lesions of the canthi and lids are treated with orthovoltage techniques. Low-energy electrons might seem advantageous compared with orthovoltage x-rays from a theoretic standpoint, but they require larger portals (~2 cm greater) because of low doses at the beam edges; it is more difficult to protect the eyeball owing to the production of high-energy x-rays in metal eye shields, and they are two to three times more expensive.[3] Additionally, Lovett and associates[31] reported a significantly lower rate of local control for basal cell carcinoma 1.1 to 5.0 cm in diameter treated at the Mallinckrodt Institute of Radiology (St. Louis) with electron beam compared with orthovoltage x-rays. A set of eye shields is essential for treatment of these lesions and gives nearly complete protection of the eyeball. Radiation therapy should not be attempted without availability of these shields (Fig. 25-27).

Amdur and coworkers[3] compared the dose distribution of 250 kVp x-rays and 6- to 20-MeV electron beam using a face phantom constructed out of solid pieces of water-equivalent epoxy to simulate the irradiation treatment of an eyelid cancer. The doses that the cornea, lens, and retina would receive beneath the midpoint of the inferior hemisphere of the shield were measured using thermoluminescent and film dosimetry. They noted that for 6- to 8-MeV electrons, the cornea dose was two to four times higher than with 250-kVp x-rays (Table 25-2). Corneal and lens doses rose rapidly with increasing electron-beam energy such that with 10- to 20-MeV electrons, the shield would provide relatively poor ocular protection. An ion chamber and film dosimetry were used to determine the isodose profiles of 250-kVp x-rays and 6-MeV electron beams for a 3-cm diameter field collimated on the surface. With 250-kVp x-rays, the 95% isodose area was 32% wider than with 6-MeV electrons (Fig. 25-28). If electrons are used, therefore, the fields must be enlarged 1.0 to 1.5 cm in all directions and bolus must be applied.

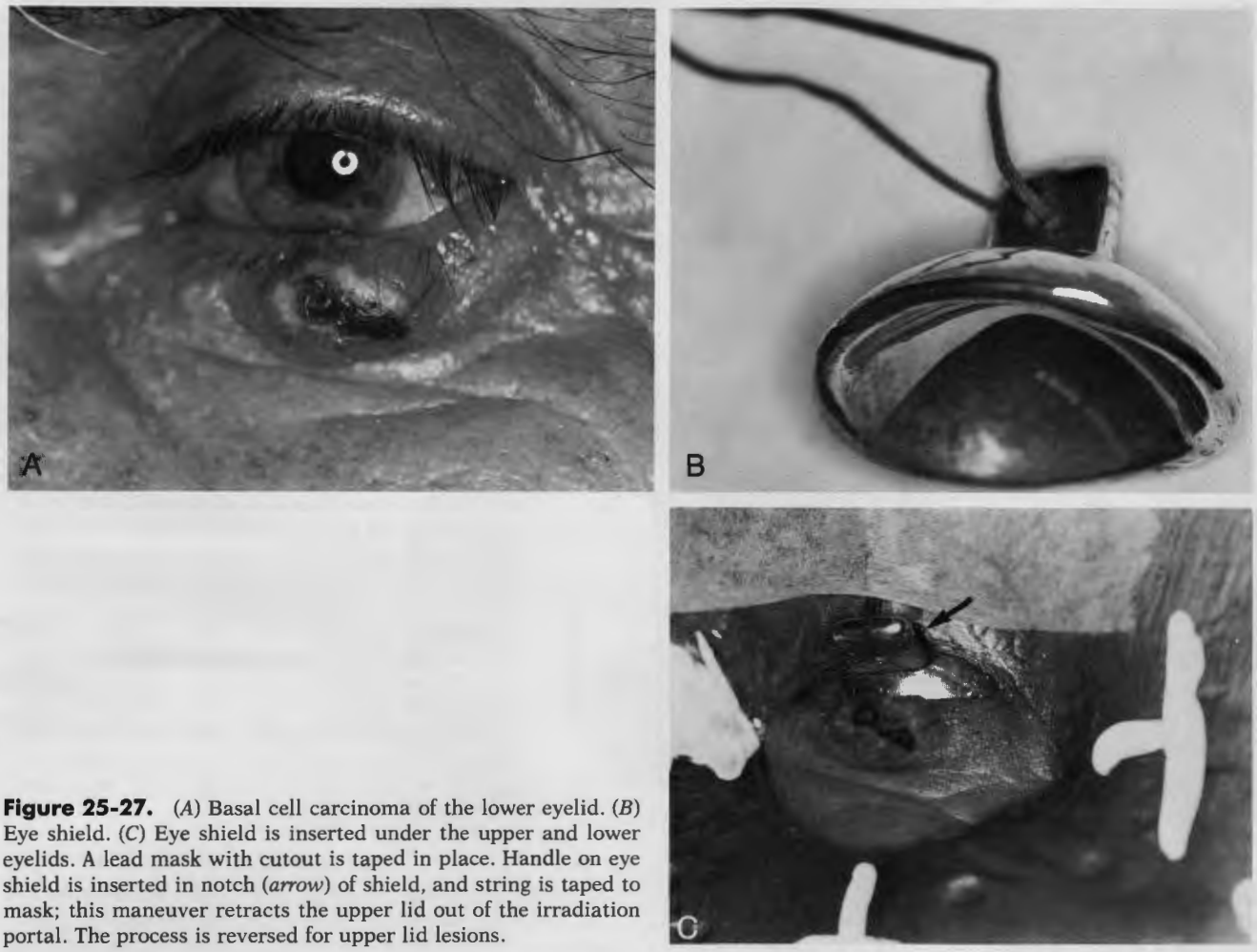

Figure 25-27. (*A*) Basal cell carcinoma of the lower eyelid. (*B*) Eye shield. (*C*) Eye shield is inserted under the upper and lower eyelids. A lead mask with cutout is taped in place. Handle on eye shield is inserted in notch (*arrow*) of shield, and string is taped to mask; this maneuver retracts the upper lid out of the irradiation portal. The process is reversed for upper lid lesions.

Additionally, the dose must be increased 10% to 15% to account for the difference in radiobiologic effectiveness (RBE). They concluded that, because of the ease of eye shielding and the ability to minimize field size, kilovoltage x-rays were the beam of choice for early skin cancer near the eye, as well as for other anatomic sites.

A lead face mask is prepared to sharply limit the radiation field and to reproduce the exact treatment portal each day (see Chap. 14). Since the treatment portals are irregular in outline, each one is calibrated separately. Slight reduction occurs in percentage depth dose at the edge of small orthovoltage beams collimated on the skin, which must be taken into account for treatment planning. These differences in depth dose give a built-in shrinking field technique, and, therefore, field reductions seldom are necessary. Additional layers of lead or lead putty must be added to the lead mask to further eliminate transit irradiation.

A mild conjunctivitis may occur during the treatment course due to daily instillation of anesthetic drops and the eye shield, plus the direct radiation effect on exposed palpebral and bulbar conjunctiva. The irradiation dose to the eyelid over the eye shield and within the field is higher than the given dose as a result of backscatter off

TABLE 25-2. Ocular Protection: Dose Beneath the Eye Shield*

Structure	Depth (mm)	250 kVp x-ray (HVL 1.4 mm Cu)	Electron-Beam Energy (MeV)						
			6	8	10	12	14	17	20
Cornea	1	10%	18%	37%	64%	75%	93%	98%	102%
Lens	8	9%	9%	19%	36%	46%	61%	70%	87%
Retina	23	10%	10%	22%	22%	21%	23%	25%	29%

* Dose is expressed as a percentage of the dose to depth of maximum dose deposition (Dmax).
(Amdur RJ, Kalbaugh KJ, Ewald LM, Parsons JT, Mendenhall WM, Bova FJ, Million RR. Radiation therapy for skin cancer near the eye: kilovoltage x-rays versus electrons. Int J Radiat Oncol Biol Phys 1992;23:775)

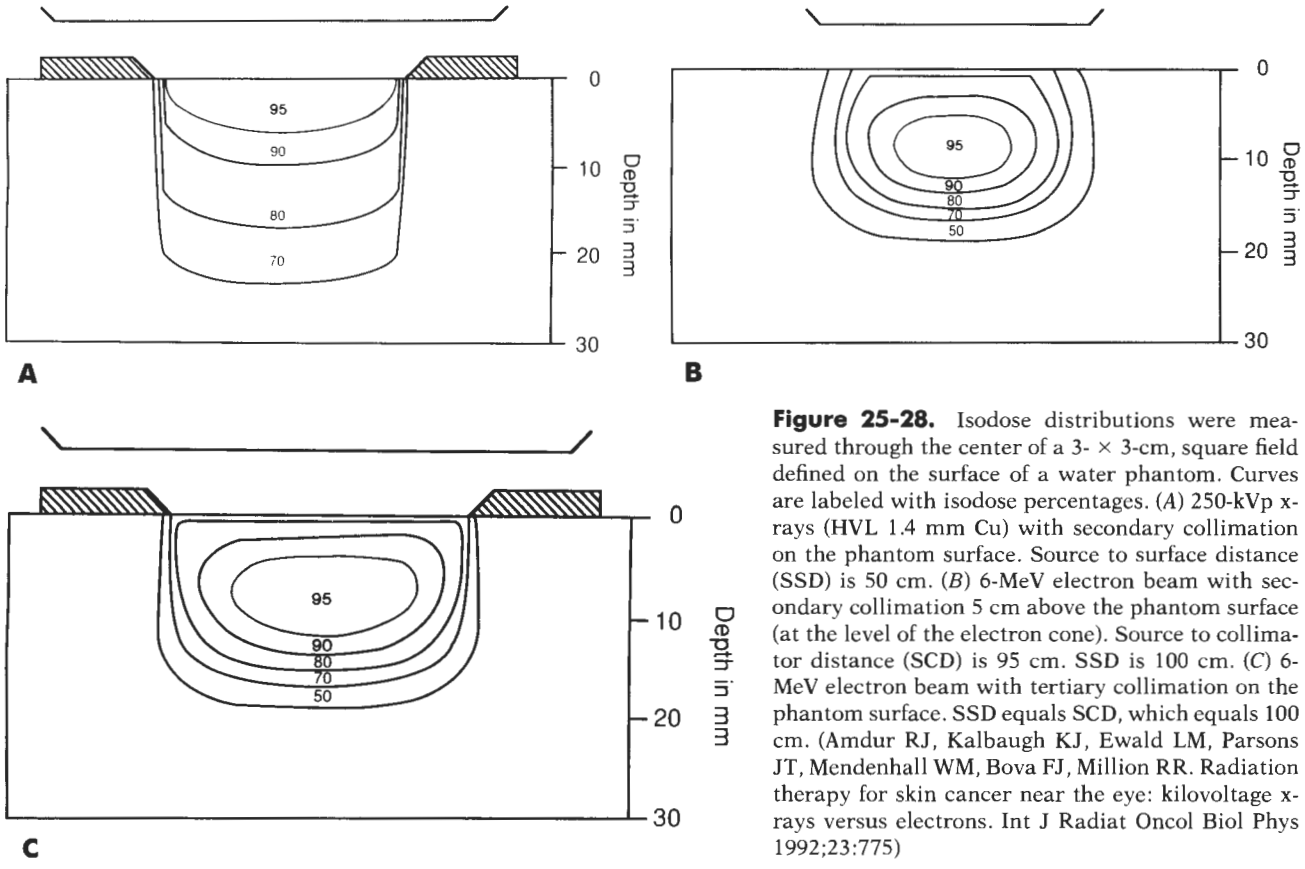

Figure 25-28. Isodose distributions were measured through the center of a 3- × 3-cm, square field defined on the surface of a water phantom. Curves are labeled with isodose percentages. (*A*) 250-kVp x-rays (HVL 1.4 mm Cu) with secondary collimation on the phantom surface. Source to surface distance (SSD) is 50 cm. (*B*) 6-MeV electron beam with secondary collimation 5 cm above the phantom surface (at the level of the electron cone). Source to collimator distance (SCD) is 95 cm. SSD is 100 cm. (*C*) 6-MeV electron beam with tertiary collimation on the phantom surface. SSD equals SCD, which equals 100 cm. (Amdur RJ, Kalbaugh KJ, Ewald LM, Parsons JT, Mendenhall WM, Bova FJ, Million RR. Radiation therapy for skin cancer near the eye: kilovoltage x-rays versus electrons. Int J Radiat Oncol Biol Phys 1992;23:775)

the eye shield for both 250-kVp x-ray and 6- to 20-MeV electron beams.[3] Lid sticking is treated with lid scrubs (a mild detergent shampoo), protective ointment at night, and an eye patch when necessary. A soothing decongestant solution (eg, Murine Plus Eye Drops or Clear Eyes Eye Drops, Ross Laboratories, Columbus, OH; Visine, Leeming/Pacquin, New York) will help relieve the itching and burning. The eyelashes usually fall out during the treatment course and usually do not regrow. The lacrimal apparatus will continue to function during therapy, but at a reduced rate. After irradiation, the lacrimal drainage system returns to near normal unless compromised by tumor or biopsy (Fig. 25-29). The lid should function normally unless there has been extensive destruction of muscle and tarsal plate by the cancer.

Mild degrees of ectropion produced by the tumor may disappear after radiation therapy, but a more severe degree of ectropion produced by the tumor usually will remain after successful treatment and may require reconstruction.

The permanent loss of eyelashes does not seem to produce any serious functional problems. (See Chap. 13 for a full discussion of the effects of radiation therapy on the eye and periorbita.)

The skin of the eyelids is thin and delicate, and fractionation schedules of 3 to 5 weeks that employ relatively small doses per fraction should be adopted for optimal results.

NOSE. Techniques for irradiation of nasal lesions vary from simple to highly individualized and complex treatments. We prefer the preparation of a face mask for most *en face* portals for orthovoltage and electron-beam therapy. Lead strips covered with wax may be inserted into the nares to reduce the transit dose to normal tissues when orthovoltage or electrons are used. A combination of photons and electrons may be used in certain situations to reduce depth dose. Supervoltage beams with bolus are useful when bone or cartilage is involved in order to gain a more homogeneous irradiation and avoid the increased dose in bone and cartilage associated with orthovoltage therapy. When supervoltage or low-energy electrons are used, a bolus is necessary to achieve full surface dose; uninvolved skin areas may not need a bolus. Lesions of the tip of the nose and nasal alar fold are frequently more extensive than judged by palpation, and treatment volumes must be generous.

There may be multiple small foci of cancer scattered over the nose and adjacent cheek with normal intervening skin. It is usually better to encompass all lesions in a single portal rather than to use multiple tiny adjacent portals.

Cartilage or bone necrosis should be a rare event with properly fractionated radiation therapy. Tumor that penetrates and destroys bone or cartilage may create a sinus between the skin and nasal cavity. This defect may contract and seal over after radiation therapy, or the sinus may remain open (Fig. 25-30). Surgical correction may be necessary if the defect is symptomatic (eg, whistling noises). Advanced nasal lesions may be successfully cured. The appearance is far from normal but is more satisfactory than total rhinectomy.

EAR. Small lesions of the pinna may be easily treated with single-portal orthovoltage irradiation. Large lesions, especially those invading cartilage and in-

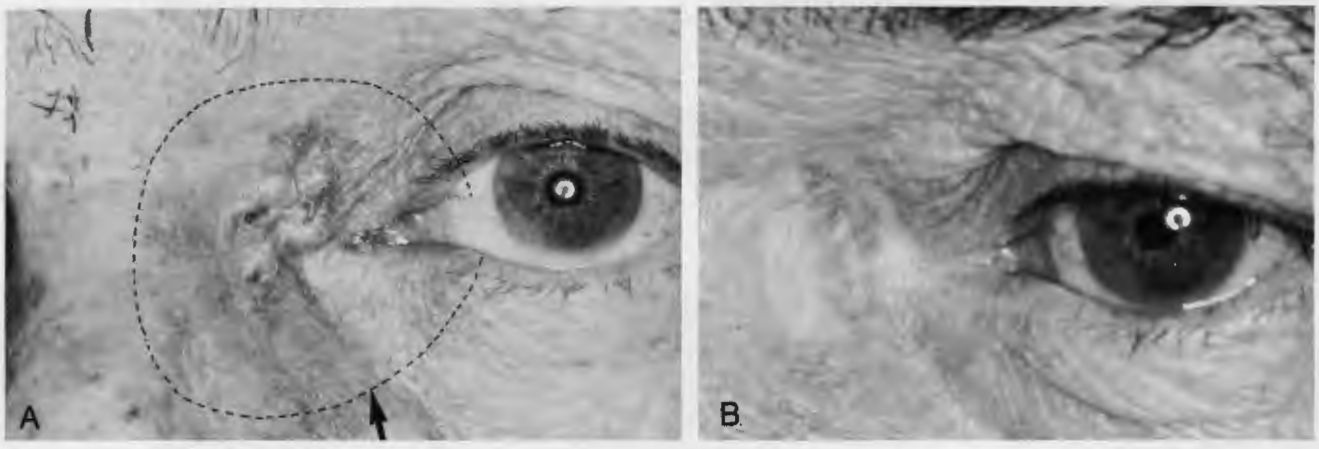

Figure 25-29. (*A*) A 60-year-old man had basal cell carcinoma of the inner canthus. The lesion was tethered to the periosteum. Treatment plan was 5500 cGy over 6 weeks, 250 kV, 3.0 Cu HVL. Approximately 1.5 cm of each lid was included in the treatment. Dashed line indicates borders of portal. (*B*) Appearance 10 months after treatment. Minimal tearing occurred, even though the proximal lacrimal system was included. No evidence of disease was seen at 3 years.

volving the postauricular sulcus, are frequently treated with supervoltage beam and a wax bolus to ensure homogeneous irradiation and reduce the differential absorption in bone and cartilage. Angled wedge fields, a three-field technique, or mixed beams will reduce irradiation to normal structures deep to the ear (Fig. 25-31). Lesions located in the concha and the external auditory canal are more difficult to control and have vague borders; surgical resection with postoperative radiation therapy may be advantageous in the infiltrative, ulcerated lesions.

UPPER LIP. Lesions greater than 1 cm often involve the vermilion or the commissure of the lip or extend near the base of the columella or alar cartilages. They may be treated with external-beam irradiation, interstitial im-

Figure 25-30. (*A*) Advanced basal cell carcinoma of the nose with extension to the cartilage and bone of nose, left lower lid and inner canthus, and right inner canthus. Patient refused rhinectomy. Treatment plan was 4500 cGy, 250 kV, and 1500 cGy, cobalt-60, with a beeswax bolus, for a total of 6000 cGy over 7 weeks. (*B*) At 3 years, no evidence of disease was found. There are two slit-like nasal–dermal sinuses that are asymptomatic. The patient remains alive and disease–free 7 years after irradiation.

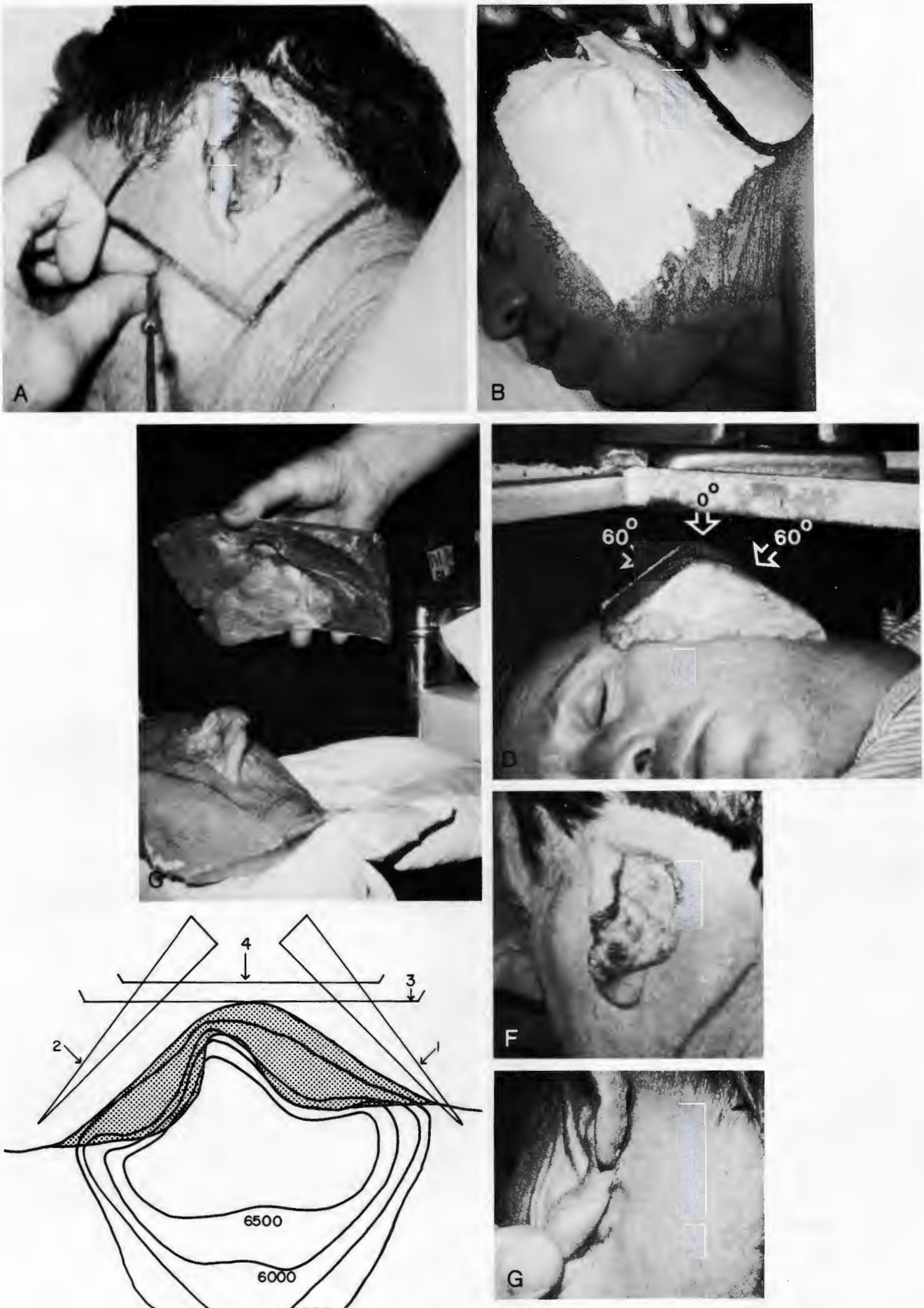

Figure 25-31.

plant, or a combination of both (see Figs. 25-19 and 25-32). A lead shield is inserted behind the upper lip to reduce transit irradiation when external-beam therapy is used; the shield is coated with wax. A gauze roll is inserted behind the upper lip at the time of the implant to reduce gingival irradiation. The dose to the lens from an upper lip implant is calculated to be 100 to 200 cGy over 6 days when the primary lesion receives 6000 cGy at 0.5 cm from a 3 × 1.5-cm single-plane implant.

SCALP. Small scalp lesions are usually managed by excision, but some lesions, although superficial, may involve an extensive area. The latter are usually managed by radiation therapy (Fig. 25-33). Advanced, destructive lesions or multiple invasive lesions usually are treated by radiation therapy; the treatment plans are individualized. Electrons are an advantage, but a variety of photon or electron beams can be mixed for the desired effect (see Figs. 25-12 and 25-34). A certain amount of brain irradiation is unavoidable in treatment of massive lesions.

TEMPLE. Small and moderate-sized lesions (2 to 3 cm) are usually managed by excision. Squamous cell carcinomas of the temple area are particularly prone to local and regional recurrence after surgical excision and should be watched closely. If the margins are close or positive, postoperative radiation therapy should be considered rather than reexcision. The larger carcinomas should be considered for radiation therapy (see Fig. 25-11). Electrons are advantageous to avoid unnecessary brain irradiation.

PREAURICULAR AREA (CHEEK). The majority of the lesions in the preauricular area present early and can be successfully managed by a surgical modality. The advanced lesions require careful staging and treatment planning, however, since they frequently invade the parotid, the pinna, and the external and internal auditory canals; approximate or invade the facial nerve; and invade the zygoma or mandible. Some may be cured by radiation therapy alone in spite of cartilage and bone invasion (see Figs. 25-9 and 25-21). If feasible, patients with clinical evidence of nerve invasion should be operated on to remove grossly involved nerves before irradiation.

The radiation treatment plan often is a lateral supervoltage external beam with a wax bolus to provide surface dose. A combination of photons and electrons or electrons alone produce the best distributions. The initial portals should be generous, and the depth-dose specification should be adequate.

Lymph Node Metastases

In the early years, we had the opportunity to observe several patients with skin cancer metastatic to lymph nodes of the parotid area that was managed by parotidectomy. Recurrence in the parotid area and ipsilateral neck seemed to be the rule rather than the exception. Attempted salvage after recurrence was associated with a low rate of success and excessive morbidity. Parotidectomy followed routinely by postoperative radiation therapy became the standard management. The entire ipsilateral neck is electively treated for subclinical disease after two failures were observed in the low neck just below the treatment portals. Before the availability of electrons, the irradiation was delivered with superior and inferior, angled, cobalt-60 (^{60}Co) portals. Since 1978, a tailored ipsilateral portal usually has been employed, and a combination of photons and electrons is selected to irradiate the anatomic areas at risk (see Chap. 27).

When the surgical margins are free of disease, the control rate is uniformly good with 6000 cGy over 6 to 7 weeks to the parotid area and 5000 cGy to the undissected neck. When the treatment margins are close or positive, however, full radical doses—6500 to 7000 cGy—are advocated. Reducing fields are used when possible, and interstitial implant boosts may be used in selected cases. The rates of disease control within the parotid area analyzed by surgical margins were as follows: negative margins, 24 of 24; positive margins, 6 of 10; and unknown, 2 of 2.[56]

Metastasis to lymph nodes of the parotid area may be managed by radiation therapy alone for a variety of reasons, with a significant success rate. The control rate related to the stage of disease is as follows[56]: N1, two of five; N2A, one of one; N2B, two of three; N3A, one of four. An interstitial implant is desirable as part of the treatment unless tumor extends to the deep lobe and parapharyngeal space. The interstitial needles usually penetrate the tragal cartilage to obtain margins. High-dose preoperative radiation therapy, 6000 to 8000 cGy, followed by parotidectomy, is a reasonable approach for borderline operable cases.

Combined Treatment Policies

Combined treatment is recommended for some advanced skin lesions or difficult recurrent lesions, but little information exists on the success rate. The operation should be performed first to take advantage of frozen section control of the excision. Reconstruction should be as simple as possible to avoid delay in the start of radiation therapy. In particular, thick flaps should be avoided and split-thickness skin grafts used when possible. Local flaps add to the risk of regional implantation of tumor cells and may greatly increase the amount of tissue to be irradiated.

Follow-Up

It is not practical to insist on frequent or long-term follow-up for the majority of patients with small skin cancers. Patients with a significant risk for recurrence or

◄ **Figure 25-31.** (*A*) Squamous cell carcinoma of the left ear with cartilage invasion (patient was blind in the right eye). Treatment plan was 6500 cGy over 7½ weeks, cobalt-60, with beeswax bolus, three-field technique. Superior and inferior portals angled 60 degrees with wedges, and a straight lateral open field (0 degrees). (*B*) Preparation of plaster mold. (*C*) Plaster cast. (*D*) Beeswax bolus in place. (*E*) Isodose distribution. Stippled area represents beeswax compensator. The dose to the midline was approximately 5000 cGy over 7½ weeks. (*F*) Appearance at 4000 cGy. (*G*) No evidence of disease was seen at 5½ years. The patient remains alive and disease–free 13½ years after irradiation.

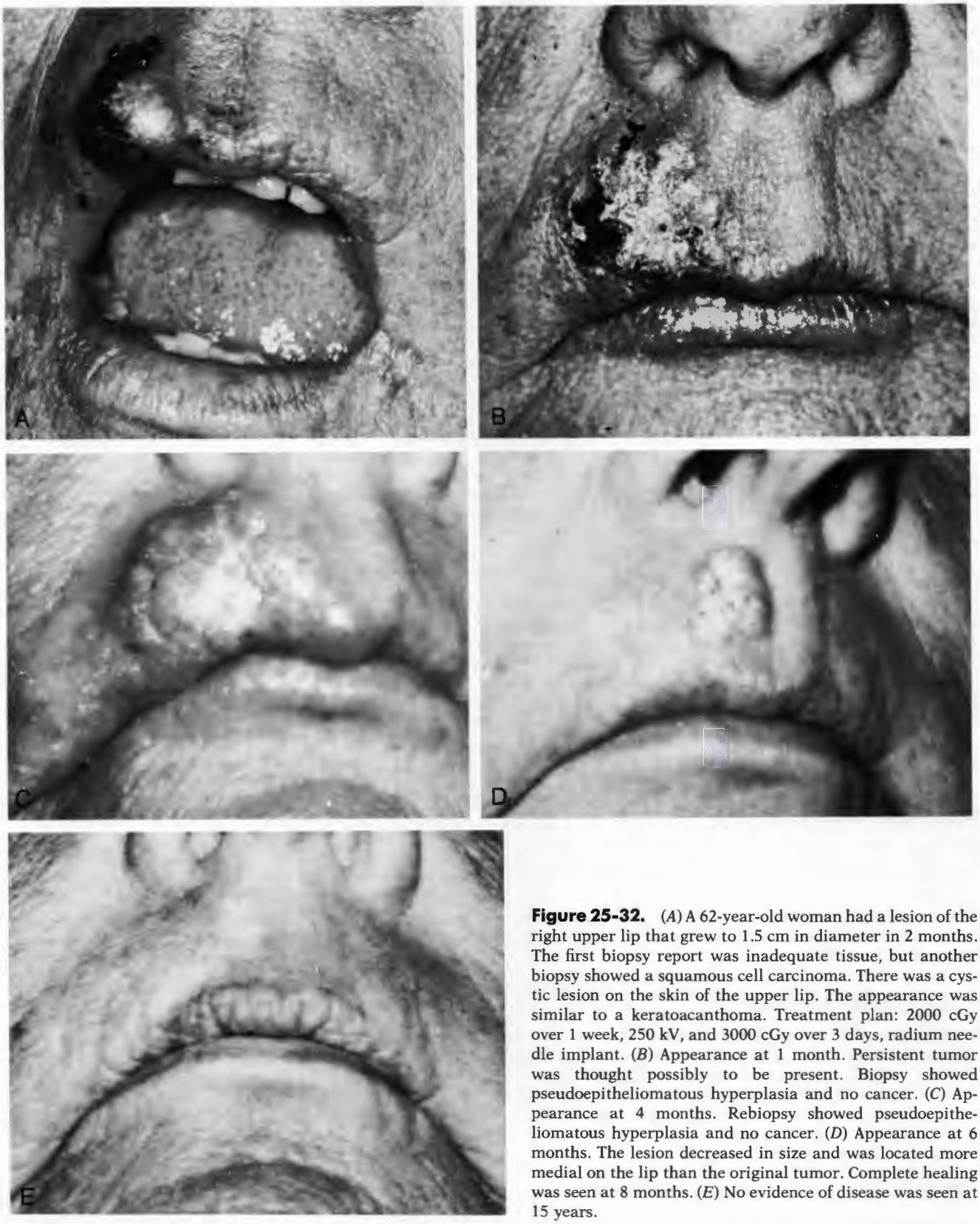

Figure 25-32. (*A*) A 62-year-old woman had a lesion of the right upper lip that grew to 1.5 cm in diameter in 2 months. The first biopsy report was inadequate tissue, but another biopsy showed a squamous cell carcinoma. There was a cystic lesion on the skin of the upper lip. The appearance was similar to a keratoacanthoma. Treatment plan: 2000 cGy over 1 week, 250 kV, and 3000 cGy over 3 days, radium needle implant. (*B*) Appearance at 1 month. Persistent tumor was thought possibly to be present. Biopsy showed pseudoepitheliomatous hyperplasia and no cancer. (*C*) Appearance at 4 months. Rebiopsy showed pseudoepitheliomatous hyperplasia and no cancer. (*D*) Appearance at 6 months. The lesion decreased in size and was located more medial on the lip than the original tumor. Complete healing was seen at 8 months. (*E*) No evidence of disease was seen at 15 years.

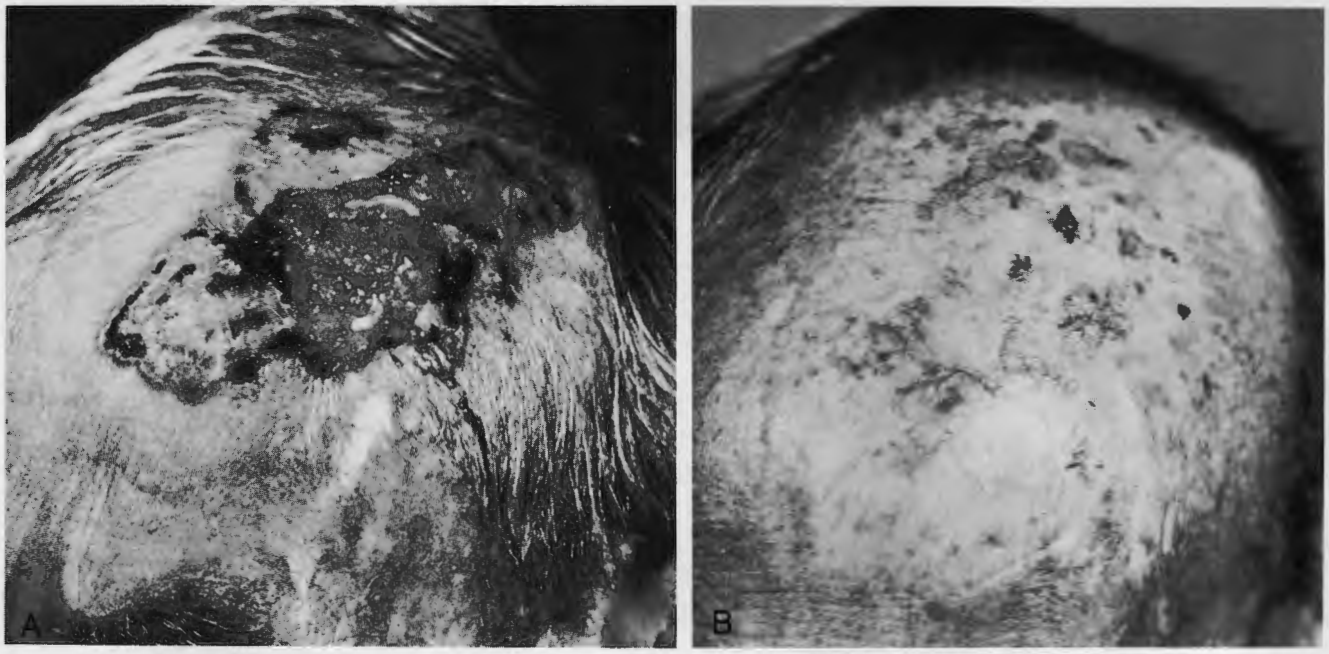

Figure 25-33. (*A*) Squamous cell carcinoma of the scalp treated with radium mold. (*B*) At 4 years, no evidence of disease was found. (Courtesy of R. L. Lindberg, MD, Department of Radiation Therapy, M.D. Anderson Hospital and Tumor Institute, Houston)

complication, however, should have follow-up every 1 to 3 months for 2 years, and less often thereafter.

Irradiated lesions may not disappear for a few weeks to even months after completion of therapy; as long as they are regressing, biopsy is withheld (Fig. 25-35).

The diagnosis of recurrence usually is obvious, but some are heralded by paresthesia and are difficult to target. Metastases to regional lymph nodes may appear after 2 years and may be confused with a parotid neoplasm, or regarded as an unknown primary lesion.

Pseudorecidivation

Pseudorecidivation is an unusual process that is infrequently seen after irradiation of skin cancer. Usually occurring within 2 weeks of the completion of treatment, pseudorecidivation, or pseudorecurrence, consists of the appearance of a raised lesion on the previously irradiated skin. The new lesion may arise at the site of the original cancer or at the periphery of the field. The lesion may be skin-colored, erythematous, yellow, or yellow brown; it may be smooth or verrucous in texture.[24] Biopsy reveals thickening of the prickle-cell layer (acanthosis) and stratum corneum (hyperkeratosis) and epidermal inclusion cyst formation. The lesions regress spontaneously, usually within 2 to 3 months. No treatment is indicated. Vaeth[58] reported five cases of pseudorecidivation, all of which spontaneously disappeared within 12 weeks; tumor recurrence was not observed in any of the five patients. To avoid unnecessary therapy, it is important to recognize that the lesion is benign and self healing (see Fig. 25-32).

Management of Recurrence

Although the overall risk of recurrence is reported to be small, the problem is significant. Microscopically controlled excision is especially useful for the difficult recurrent lesions. Radiation therapy may be used to advantage in certain cases because of the ability to cover rather generous potential areas of spread, both for horizontal and vertical spread (Figs. 25-36 and 25-37). The management of recurrent lesions is best placed in experienced hands, since a second recurrence often predicts eventual failure to obtain control.

Multiple sites of recurrence or new lesions are essentially incurable and test the imagination of the physicians to prescribe reasonable therapy. Frequent observation may be the only sensible approach, with palliative treatment added only when essential.

TREATMENT RESULTS

Results According to Histologic Type

Basal Cell and Squamous Cell Carcinoma

Treatment results for the various therapies are practically impossible to compare because of the selection for various treatments based on the size of the lesion, its location, and prior therapy (whether untreated or recurrent). In addition, for patients with multiple lesions, it is often difficult to distinguish a treatment failure from a new cancer.

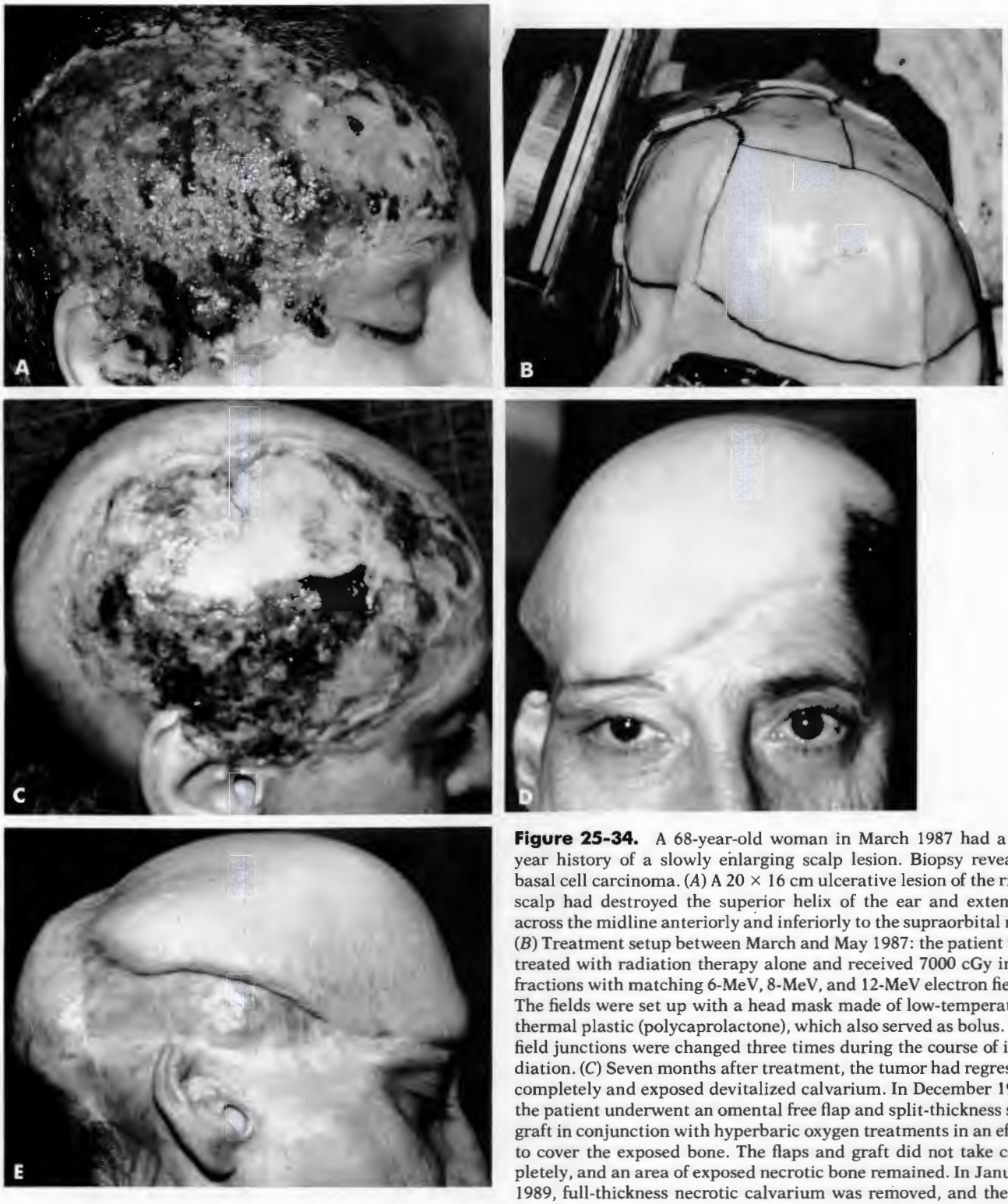

Figure 25-34. A 68-year-old woman in March 1987 had a 10-year history of a slowly enlarging scalp lesion. Biopsy revealed basal cell carcinoma. (*A*) A 20 × 16 cm ulcerative lesion of the right scalp had destroyed the superior helix of the ear and extended across the midline anteriorly and inferiorly to the supraorbital rim. (*B*) Treatment setup between March and May 1987: the patient was treated with radiation therapy alone and received 7000 cGy in 35 fractions with matching 6-MeV, 8-MeV, and 12-MeV electron fields. The fields were set up with a head mask made of low-temperature thermal plastic (polycaprolactone), which also served as bolus. The field junctions were changed three times during the course of irradiation. (*C*) Seven months after treatment, the tumor had regressed completely and exposed devitalized calvarium. In December 1987, the patient underwent an omental free flap and split-thickness skin graft in conjunction with hyperbaric oxygen treatments in an effort to cover the exposed bone. The flaps and graft did not take completely, and an area of exposed necrotic bone remained. In January 1989, full-thickness necrotic calvarium was removed, and the defect was successfully covered with a latissimus dorsi free flap. (*D* and *E*) On follow-up in December 1990, the tumor site had healed completely. The patient had no evidence of recurrent basal cell carcinoma when last seen in December 1991.

Figure 25-35. (*A*) Basal cell carcinoma of the right lower lid (2.5 × 1.0 cm). The patient had a history of slow growth of the lesion for longer than 10 years. Treatment was with 250 kV, 5 mm Cu filtration. The dose was 6500 cGy in 33 fractions over 5½ weeks; the prescribed dose today would be 5000 cGy over 4 weeks. (*B*) Persistent abnormality 2 months after completion of treatment (*arrows*). The tumor regressed slowly, and finally disappeared completely about 6 months after completion of treatment. (*C*) Appearance at 14 years. Patient had mild, intermittent tearing.

Most reports claim 95% or greater success rates for basal cell carcinomas and 90% or greater rates for squamous cell carcinomas. The probability of cure for microcystic basal cell carcinoma is the same as for the more common variety of basal cell carcinoma. When comparing the various modalities, a difference of only a few percentage points exists. The success rate may be slightly inflated owing to the large number of early-stage lesions, the lack of long-term follow-up, and the difficulty in discerning local recurrence versus a new skin cancer. Almost all of the published data have been analyzed without using a staging system, so that it is virtually impossible to accurately compare the results from these series. Physicians who deal with a greater percentage of the more complicated, advanced-stage, and often recurrent skin cancer are less optimistic about the management of skin cancer.

Rigel and coworkers[47] reviewed the results for 2960 basal cell carcinomas treated by microscopically controlled excision with a 5-year follow-up. The overall recurrence rate was 2.6%. A group of lesions at high risk for recurrence (ie, 10%) was identified based on size (more than 4 cm in diameter); anatomic location (eg, periauricular site); number of excisions to obtain tumor-free margins; and prior therapy.

Lovett and associates[31] reviewed a series of 339 patients with basal or squamous cell carcinoma of the skin treated with irradiation alone at Mallinckrodt Institute of Radiology. The data were stratified according to prior treatment, histologic type, and tumor diameter; a formal staging system was not used. Local control with irradiation is listed in Table 25-3. The authors noted a higher local control rate for lesions 1.1 to 5 cm in diameter treated with orthovoltage x-ray compared with electron beam or a combination of beam energies (Table 25-4). Few patients in this series had lesions more than 5 cm in diameter. A multivariate analysis of the data revealed the following factors to significantly influence local control: type of beam ($P < .001$), dose per fraction ($P = .001$), prior treatment ($P = .01$), and tumor diameter ($P = .043$). Histologic type, tumor dose, and gender did not influence local control in the multivariate analysis.

Mendenhall and colleagues[39] reviewed the University of Florida experience of 99 patients with 100 T2–4 skin carcinomas who were treated by irradiation between 1964 and 1983. There were 42 basal cell carcinomas, 55 squamous cell carcinomas, and three metatypical basal cell carcinomas. Follow-up ranged from 2 to 21 years. Bone and cartilage invasion was determined roentgenographically or clinically; perineural invasion was as-

Figure 25-36. In 1972, a basal cell carcinoma was completely excised from the left nasolabial crease. In 1979, a basosquamous cell carcinoma was completely excised from the left alar rim, followed by reconstruction with a nasolabial flap. In 1980, the woman (then 85 years old) had regrowth of the mass in the left side of the nose accompanied by numbness of the upper lip. Biopsy revealed poorly differentiated squamous cell carcinoma. (*A*) CT shows soft tissue mass in the left nasal area. The anterior wall of the antrum is ill-defined adjacent to the mass, but there is no mass within the antrum. (*B*) There was a 4.0- × 3.5-cm indurated mass arising from the nasolabial fold and visible tumor in the nasal vestibule. The anterior portal is shown. The primary lesion received 7950 cGy total dose over 7½ weeks. Portal reductions were made after 5000 cGy, 6000 cGy, and 7125 cGy; 20-MeV electrons were used for 6000 cGy, 17-MeV electrons for 1000 cGy, and 250 kV for the final 825 cGy. The left upper neck and left parotid lymph nodes were electively irradiated to 5000 cGy. (*C*) Appearance at 17 months. The patient died without evidence of recurrent cancer 6 years after irradiation.

Figure 25-37. A 69-year-old man had squamous cell carcinoma of the left cheek that had been excised; the margins were free of tumor. Nine months after excision the surgical site began to slowly enlarge. Biopsy 3 months later revealed poorly differentiated squamous cell carcinoma. (*A*) A 1-cm ulceration existed with surrounding induration measuring 4 × 5 cm. (*B*) Treatment plan to the primary site was electron-beam irradiation, 14 MeV, 5000 cGy over 5 weeks. The left lower neck received 8-MV x-ray, 5000 cGy given dose over 5 weeks. A single-plane radium needle implant. Note that needles penetrate ear cartilages. (*C*) No evidence of disease was seen at 9 years.

sessed clinically. Recurrent lesions were staged according to the findings at the time of recurrence when they presented for retreatment. Local control rates after radiation therapy (initial local control) and the ultimate local control rates, including patients successfully salvaged after local recurrence, are outlined in Table 25-5. The local control rates after irradiation for T4 lesions are presented in Table 25-6 as a function of various parameters. Photographs of some of these lesions appear throughout this chapter. Survival data are shown in Table 25-7. The incidence of severe complications resulting in significant morbidity, or necessitating surgical intervention, was 5%; all occurred in patients treated for lesions that were staged T4 or were recurrent after prior treatment (Table 25-8).

Lee and associates[28] reported an update of 67 patients treated with irradiation alone at the University of Florida for 68 T4 skin cancers. Parameters included in a multivariate analysis were as follows: histologic type; primary tumor size; previous treatment; and involvement

TABLE 25-3. Local Control With Radiation Therapy: Tumor Control by Size, Histologic Type, and Presentation (339 Patients)

Size	Basal Cell, Previously Untreated	Basal Cell, Recurrent	Squamous Cell, Previously Untreated	Squamous Cell, Recurrent
≤1 cm	64/66 (97%)	22/23 (96%)	11/11 (100%)	10/12 (83%)
1.1–3 cm	71/75 (95%)	27/36 (75%)	19/21 (90%)	7/13 (54%)
3.1–5 cm	11/13 (85%)	7/9 (78%)	7/8 (88%)	6/9 (67%)
>5 cm	12/13 (92%)	1/2 (50%)	3/5 (60%)	6/11 (55%)
Size not specified	4/4 (100%)	1/1 (100%)	0/1 (0%)	4/6 (67%)
TOTAL	162/171 (95%)	58/71 (82%)	40/46 (87%)	33/51 (65%)

Note: Mallinckrodt Institute of Radiology data.
(Lovett RD, Perez CA, Shapiro SJ, Garcia DM. External irradiation of epithelial skin cancer. Int J Radiat Oncol Biol Phys 1990;19:238)

TABLE 25-4. Carcinoma of the Skin Treated With Radiation Therapy: Comparison of External-Beam Technique—Local Control (339 Patients)

Modality	Size* ≤1 cm	1.1–5 cm	>5 cm	Not specified
BASAL CELL CARCINOMA				
Superficial x-ray	69/71 (97%)	84/90 (93%)	4/4 (100%)	3/3 (100%)
Electron beam	11/12 (92%)	16/22 (73%)	4/5 (80%)	1/1 (100%)
Combination	5/5 (100%)	13/16 (81%)	5/6 (83%)	0/0
Photons (1.2–4 MV)	1/1 (100%)	3/5 (60%)	0/0	1/1 (100%)
SQUAMOUS CELL CARCINOMA				
Superficial x-ray	12/12 (100%)	10/11 (91%)	1/1 (100%)	0/0
Electron beam	3/4 (75%)	7/10 (70%)	3/4 (75%)	0/1 (0%)
Combination	4/5 (80%)	19/26 (73%)	4/8 (50%)	2/4 (50%)
Photons (1.2–4 MV)	2/2 (100%)	3/4 (75%)	1/3 (33%)	2/2 (100%)

* Significance levels: basal cell carcinoma, 1.1–5 cm, superficial x-ray (84/90) vs electron beam/combination (29/38), $P = .013$; squamous cell carcinoma, ≤1 cm, superficial x-ray (12/12) vs electron beam/combination (7/9), $P = .17$; squamous cell carcinoma 1.1–5 cm, superficial x-ray (10/11) vs electron beam/combination (26/36), $P = .41$.
Note: Mallinckrodt Institute of Radiology data.
(Adapted from Lovett RD, Perez CA, Shapiro SJ, Garcia DM. External irradiation of epithelial skin cancer. Int J Radiat Oncol Biol Phys 1990;19:238)

TABLE 25-5. T2–4 Carcinoma of the Skin Treated by Radiation Therapy: Local Control Rates at 5 Years*

Prior Treatment	T Stage	Lesions	Local Control at 5 Y (%) Initial	Ultimate
Previously untreated	T2	17	93	100
	T3	12	83	100
	T4	27	54	79
Recurrent	T2	7	100	100
	T3	11	72	88
	T4	26	29	53

* Actuarial method.
(Mendenhall WM, Parsons JT, Mendenhall NP, Million RR. T2–T4 carcinoma of the skin of the head and neck treated with radical irradiation. Int J Radiat Oncol Biol Phys 1987;13:976)

TABLE 25-6. 5-Year Local Control After Irradiation: Analysis of Prognostic Factors for T4 Lesions*

Parameter	Group	Previously Untreated		Recurrent	
		Patients	Control Rate (%)	Patients	Control Rate (%)
Histologic type	Squamous cell carcinoma	13	60§	13	35‖
	Basal cell carcinoma	14	46§	13	25‖
Prognostic factors (extension to bone, cartilage, or nerve)	1 prognostic factor	20	58¶	19	44#
	≥2 prognostic factors	7	43¶	7	0#
Size	≤5 cm	15	52	15†	39
	>5 cm	12	55	7†	30
Cartilage destruction	Alone	14	64**	7	34
	Plus 1 or more other prognostic factors	7	43**	1	0/1‡
Nerve involvement	—	6	33††	6	0††
Bone involvement	—	9	55‡‡	13	16‡‡

* Actuarial method.
† Excludes four lesions for which the size was not stated.
‡ Absolute calculation.
Note: § $P = .6$; ‖ $P = .4$; ¶ $P = .21$; # $P = .018$; ** $P = .28$; †† $P = .54$; ‡‡ $P = .35$.
(Mendenhall WM, Parsons JT, Mendenhall NP, Million RR. T2–T4 carcinoma of the skin of the head and neck treated with radical irradiation. Int J Radiat Oncol Biol Phys 1987;13:976)

of bone, nerve, cartilage, or skeletal muscle. Three important parameters were noted: recurrent lesions resulted in poorer ultimate local control and cause-specific survival rates ($P = .01$); bone involvement predicted decreased ultimate local control and cause-specific survival ($P = .01$); and clinical evidence of nerve invasion was associated with diminished ultimate local control and cause-specific survival ($P = .02$).[28]

Mendenhall and colleagues[38] reported a series of 25 patients with carcinoma of the skin with clinical evidence of perineural invasion before treatment at our institution. Patients were treated between 1966 and 1983, and all had follow-up for at least 5 years. Eight patients had previously untreated lesions and 17 were recurrent after prior therapy. There were 15 squamous cell carcinomas, 9 basal cell carcinomas, and 1 metatypical basal cell carcinoma. Treatment at the University of Florida consisted of irradiation alone (16 patients) or combined irradiation and surgery (9 patients). The rates of disease control at the primary site and the ultimate local control rates are depicted in Table 25-9. The actuarial rates of local control and cause-specific survival for the treatment groups are presented in Figures 25-38 and 25-39. All recurrences were noted within 5 years of treatment. Fifteen patients died because of cancer: 13 patients with local recurrence alone, 1 patient with recurrence at the primary site and in the neck, and 1 patient with distant metastasis alone.

Levine[29] reported the results for the surgical management of 60 patients with advanced skin cancer. There

TABLE 25-7. T2–4 Carcinoma of the Skin Treated by Radiation Therapy: Cause-Specific Survival Rates at 5 Years*

Prior Treatment	T Stage	Patients†	Cause-Specific 5-Y Survival (%)
Previously untreated	T2	17	100
	T3	11	100
	T4	27	88‡
Recurrent	T2	7	100
	T3	11	100
	T4	26	59‡

* Actuarial method.
† One patient had simultaneous T3 and T4 previously untreated lesions and is counted in the T4 category for cause-specific analysis.
‡ $P = .066$.
(Mendenhall WM, Parsons JT, Mendenhall NP, Million RR. T2–T4 carcinoma of the skin of the head and neck treated with radical irradiation. Int J Radiat Oncol Biol Phys 1987;13:978)

TABLE 25-8. T2–4 Carcinoma of the Skin Treated by Radiation Therapy: Incidence of Severe Complications

Prior Treatment	T Stage	Severe Complications/ Patients Treated*
Previously untreated	T2	0/17
	T3	0/11
	T4	3/27
Recurrent	T2	0/7
	T3	2/11
	T4	0/26
TOTAL	All	5/99 (5%)

* One patient with simultaneous previously untreated T3 and T4 lesions is included in the T4 group.
(Mendenhall WM, Parsons JT, Mendenhall NP, Million RR. T2–T4 carcinoma of the skin of the head and neck treated with radical irradiation. Int J Radiat Oncol Biol Phys 1987;13:978)

TABLE 25-9. Carcinoma of the Skin With Perineural Invasion*: Control of Disease at the Primary Site (No. Controlled/No. Treated)

Treatment Group	Previously Untreated or Recurrent	Extension to Bone or Cartilage	Excluded†	Control After Initial Treatment	Salvaged/ Attempted	Ultimate Control
Irradiation alone	Previously untreated	No	0	1/2	No data	1/2
		Yes	0	1/4	1/1	2/4
	Recurrent	No	1	1/4	0/1	1/4
		Yes	0	0/5	0/1	0/5
TOTAL		—	1	3/15	1/3	4/15
Surgery plus irradiation	Previously untreated	No	0	0/1	1/1	1/1
		Yes	0	0/1	0/1	0/1
	Recurrent	No	0	No data	No data	No data
		Yes	1	3/6	No data	3/6
TOTAL		—	1	3/8	1/2	4/8

* Clinical evidence of perineural invasion.
† Died within 2 y of treatment with primary site continuously disease-free.
(Mendenhall WM, Parsons JT, Mendenhall NP, Brant TA, Stringer SP, Cassisi NJ, Million RR. Carcinoma of the skin of the head and neck with perineural invasion. Head Neck 1989;11:304)

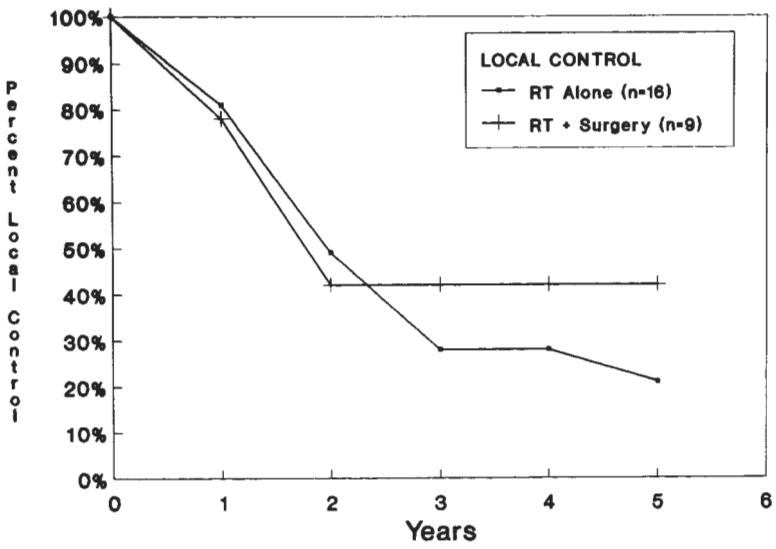

Figure 25-38. Skin carcinoma with perineural invasion: local control (life-table method). (Mendenhall WM, Parsons JT, Mendenhall NP, Brant TA, Stringer SP, Cassisi NJ, Million RR. Carcinoma of the skin of the head and neck with perineural invasion. Head Neck 1989;11:305)

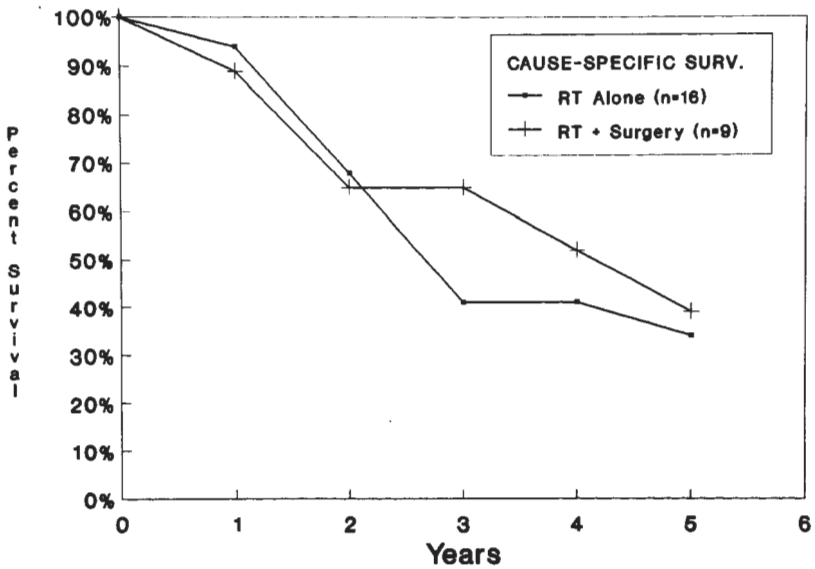

Figure 25-39. Skin carcinoma with perineural invasion: cause-specific survival (life-table method). (Mendenhall WM, Parsons JT, Mendenhall NP, Brant TA, Stringer SP, Cassisi NJ, Million RR. Carcinoma of the skin of the head and neck with perineural invasion. Head Neck 1989;11:306)

TABLE 25-10. Spindle Cell Tumors of the Skin: Results of Excision Related to Depth of Invasion

Depth of Invasion	Patients	Recurrence	Uncontrolled Recurrence	Metastases	Deaths
Dermis, subcutis	29	5	0	0	0
Muscle, bone	9	6	5	4	6

(Adapted from Evans HL, Smith JL. Spindle cell squamous carcinomas and sarcoma-like tumors of the skin: a comparative study of 38 cases. Cancer 1980;45:2696)

were 40 basal cell carcinomas and 20 squamous cell carcinomas. All were recurrent after one or more previous therapies. All lesions were 3 cm or more in maximum diameter; 39 involved cartilage, 28 involved bone, and two extended intracranially. All of these lesions were managed either by conventional surgery and total microscopic margin control (fresh-tissue technique), or by Mohs' fixed-tissue technique followed by the fresh-tissue technique. With follow-up ranging from 1 to 4 years, 53 patients had no evidence of disease, 5 were alive with disease, and 2 were dead of disease.

Spindle Cell Tumors

Evans and Smith[13] reviewed 38 cases of spindle cell tumors of the skin. The results of excision are related to the depth of invasion in Table 25-10 and to the margins of excision in Table 25-11. There was no difference in results, regardless of whether the lesion was composed of spindle cells and squamous cells or contained only the spindle cell elements.

Judging from our limited experience, spindle cell–squamous cell carcinoma of the skin is curable with radiation therapy.

Sebaceous Cell Carcinoma

Rulon and Helwig[48] reviewed 59 cases of sebaceous carcinoma of the skin; 11 patients developed recurrence after excision and 8 developed metastases to lymph nodes of the parotid area.

Merkel Cell Carcinoma

Goepfert and coworkers[18] reviewed a series of 29 patients with Merkel cell carcinoma arising from the skin of the head and neck treated at M.D. Anderson Hospital between 1966 and 1983. Twenty of 29 patients received all of their treatment at M.D. Anderson Hospital. Initial treatment of the primary cancer consisted of surgery in 12 patients, surgery and postoperative radiation therapy in 13 patients, and radiation therapy alone in 4 patients. Local recurrence developed in 25% of patients. Thirteen of 29 patients (45%) had clinically positive regional nodes; 12 patients underwent neck dissection alone (3) or combined with postoperative irradiation (9), and the nodal disease was controlled in 10 of 12 patients. Sixteen patients had clinically negative regional nodes; 12 did not receive elective neck dissection, and eight of 12 developed recurrence in the regional nodes. Four patients underwent elective neck dissection; two of four had nodes with positive pathologic results, and two patients developed nodal recurrence (one who had tumor in the specimen and one who did not). Some evidence exists that the addition of irradiation to surgery will enhance the likelihood of local–regional control.[8,43] Distant metastases were noted in 14 patients: 1 patient at presentation and in 13 patients later in the course of their disease. The cause-specific survival rates were 58% at 2 years and 21% at 5 years.

Results According to Anatomic Site

Pinna

Parker and Wildermuth[45] reported the results for 38 carcinomas of the pinna treated with radiation therapy (Table 25-12) with a follow-up of 3 to 15 years. Ten patients had cartilage invasion before treatment. No instances of chondronecrosis occurred. No local recurrences occurred above an isoeffect line connecting 4250 cGy over 2 weeks (10 fractions), 4500 cGy over 3 weeks (15 fractions), and 5000 cGy over 4 weeks (20 fractions); these schemes are similar to those recommended in Table 25-1. The local recurrence rate was 4 of 38 (11%); in one patient salvage was achieved surgically. Two patients died of lymph node metastases.

Martin and Martin,[33] as well as del Regato and Vuksanovic,[11] reported similar results for the ear.

Eyelid

Fitzpatrick and associates[16] reported the results for 447 basal cell carcinomas and 30 squamous cell carcino-

TABLE 25-11. Spindle Cell Tumors the Skin: Results of Excision Related to Margins of Excision

Margins of Excision	Patients	Recurrence	Uncontrolled Recurrence	Metastases	Deaths
Margins negative	31	5	1	2	2
Margins positive	7	6	4	2	4

(Adapted from Evans HL, Smith JL. Spindle cell squamous carcinomas and sarcoma-like tumors of the skin: a comparative study of 38 cases. Cancer 1980;45:2695)

TABLE 25-12. Radiation Therapy in Carcinoma of the Pinna*

Stage	Patients	Local Recurrence	Surgical Salvage
I	14	0	—
II	10	2	1/2
III	14	2	0/2

* Data from Parker and associates.[45] Follow-up 3–15 y.

mas of the eyelids treated by irradiation between 1958 and 1968. The average diameter was 12 mm. The local recurrence rate was 5% for basal cell carcinoma and 3% for squamous cell carcinoma. Fifteen recurrences were in the center and 10 at the edge of the lesion. No deaths due to eyelid cancer occurred, with follow-up of 3 to 13 years. The cosmetic and functional results were judged to be poor to fair in 6% of cases after 5 years' follow-up. Abraham and coworkers[1] reported a local recurrence rate of 7% for 68 patients with basal cell carcinoma of the medial canthal region treated by surgical methods.

Nose

Mazeron and associates[36] reported a series of 1676 carcinomas of the skin of the nose (1612) and nasal vestibule (64) treated with radiation therapy; all patients had at least 2 years of follow-up. Radiation therapy was delivered either by external beam with orthovoltage (781), or megavoltage (133) equipment, or by interstitial implantation (762). The overall local control rate was 93% and was related to tumor size: smaller than 2 cm, 96%; 2 to 3.9 cm, 88%; 4 cm or larger, 81%. The incidence of necrosis after treatment was 2% for skin lesions and 0% for cancer of the nasal vestibule.

Lymph Nodes of the Parotid Area

The parotid area control and survival rates for 60 patients treated at the University of Florida with carcinoma of the skin metastatic to lymph nodes of the parotid area are outlined in Table 25-13, and the absolute and cause-specific survival rates are plotted in Figures 25-40 and 25-41, respectively.[56]

Jackson and Ballantyne[26] reported a 71% 2-year cause-specific survival rate for 123 non-basal cell carcinomas requiring a parotidectomy as part of their treatment; 18% of patients had postoperative or preoperative radiation therapy. Twenty-three patients died of local or regional failure and 11 of distant metastases. Wang[59] reported the results for 28 patients, who had metastases to lymph nodes of the parotid area, treated by radiation therapy alone (25 patients) or combined radiation therapy and parotidectomy (3 patients); 2 patients had recurrent disease after initial operation. Radiation therapy usually combined a lateral wedge pair (^{60}Co) with boosts by interstitial implant or electron beam. The maximum dose in patients treated partly by implant was in the range of 8000 to 9000 cGy. The parotid area and neck control rates are shown in Table 26-14. No complications of the facial nerve, temporomandibular joint, ear, bone, or muscles were reported.

COMPLICATIONS

Surgery

True operative complications mostly involve problems with healing of flaps or split-thickness skin grafts. Reconstructive efforts may be unsatisfactory and require multiple revisions. Late complications are not likely.

Jackson and Ballantyne[26] reported dysfunction of the facial nerve in 7% of patients before operation for parotid area metastases. The nerve was preserved in 57% of patients, partially preserved in 24%, and totally sacrificed in 19%.

Taylor and associates[56] reported that 7 of 21 patients without tumor involvement of the facial nerve developed transient facial nerve palsy after surgery for metastasis to lymph nodes of the parotid area; no patient developed permanent facial nerve injury (Table 25-15).

Radiation Therapy

Primary Lesion

Acute complications vary with the anatomic site. The skin usually heals in 3 to 4 weeks after therapy for small lesions; 2 to 4 months may be required for large areas.

Late complications are site dependent. Skin damage is related to the fractionation scheme. Large tumor ulcers heal by secondary intention and often are covered by a thin, atrophic, relatively avascular epithelium with spotty pigmentation and telangiectatic vessels; these ar-

TABLE 25-13. Carcinoma of the Skin Metastatic to Parotid Area Lymph Nodes: Control of Disease in the Parotid Area and 5-Year Survival

	Parotids	Excluded*	Controlled/ Treated	Salvaged/ Attempted†	Ultimate Control	Cause-Specific 5-Y Survival‡
Surgery alone	8	0	2/8	3/6	5/8	42%
Radiotherapy alone	16	3	6/13 (46%)	0/2	6/13 (46%)	48%
Surgery and radiotherapy	37	1	32/36 (89%)	0/1	32/36 (89%)	75%

* Dead within 2 y of treatment with the parotid area continuously disease-free.

† Salvage was considered successful if the parotid area was continuously disease free for ≥1 y.

‡ Cause-specific survival was calculated by the product-limit method.

(Modified from Taylor BW, Brant TA, Mendenhall NP, Mendenhall WM, Cassisi NJ, Stringer SP, Million RR. Carcinoma of the skin metastatic to parotid area lymph nodes. Head Neck 1991;13:429)

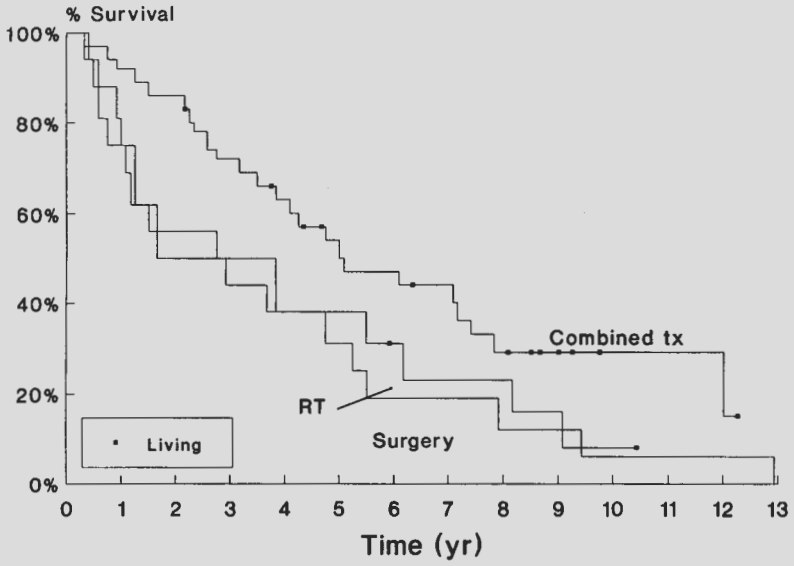

Figure 25-40. Skin carcinoma metastatic to parotid area nodes: absolute survival by treatment group (product-limit method). Survival time is indicated for each living (censored) patient. (Taylor BW, Brant TA, Mendenhall NP, Mendenhall WM, Cassisi NJ, Stringer SP, Million RR. Carcinoma of the skin metastatic to parotid area lymph nodes. Head Neck 1991;13:430)

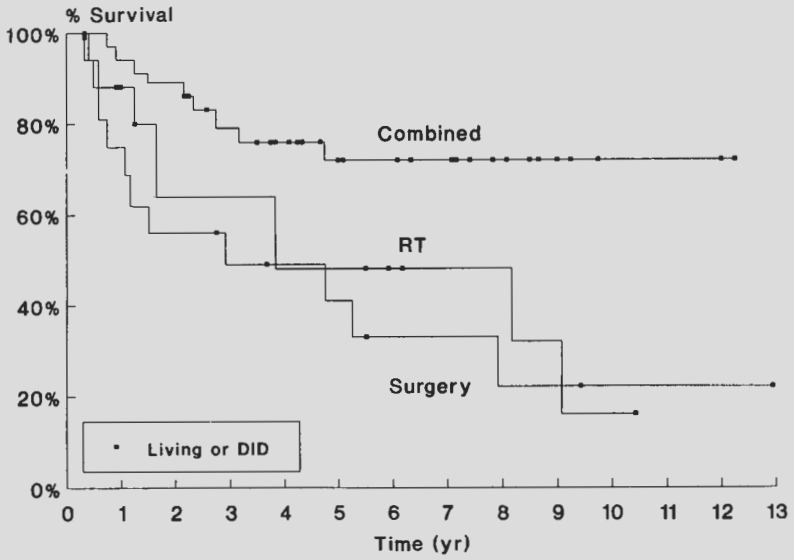

Figure 25-41. Skin carcinoma metastatic to parotid area nodes: cause-specific survival by treatment group (product-limit method). Survival time is indicated for each censored patient (either living, or died of intercurrent disease with no parotid area tumor present, at that time). (Taylor BW, Brant TA, Mendenhall NP, Mendenhall WM, Cassisi NJ, Stringer SP, Million RR. Carcinoma of the skin metastatic to parotid area lymph nodes. Head Neck 1991;13:430)

TABLE 25-14. Parotid Area Lymph Node Metastases Treated by Radiation Therapy*

Stage†	Parotid or Neck Control	Patients With No Evidence of Disease
N1	7/8	6
N2A	3/4	3
N2B	5/8	3
N3A	3/4	1
TOTAL	18/24 (75%)	13/24 (54%)

* Follow-up 2–17 y, 11 patients died of disease (6 died of parotid or neck recurrence, 5 died of distant metastases).

† See source article for details of staging system.[58]

(Adapted from Wang CC. The management of parotid node metastases by irrodiation. Cancer 1982;50:224)

TABLE 25-15. Status of Cranial Nerve VII as Related to Control of Disease in the Parotid Area in Patients Treated With Combined Surgery and Radiation Therapy*

Status of Nerve	Parotid Area Controlled/Treated
No injury	14/14
Transient injury after surgery	7/7
Nerve preserved with gross tumor involvement	1/2
Partial or complete sacrifice for gross tumor invasion	10/13

* 35 patients with 36 parotids at risk. Data from Taylor and coworkers.[56]

eas do not have sweat glands, sebaceous glands, or hair. Needless to say, these areas do not tolerate trauma or infection well (see Chap. 13 for comments on cartilage and bone).

Patients with cartilage invasion may report increased tenderness during the course of radiation therapy, but most report a decrease or no change in symptoms. Antibiotics may be used to treat infection.

Patients with obvious bone invasion and destruction are usually relatively asymptomatic and remain that way throughout therapy. Osteoradionecrosis of the calvarium occurred in past years when improper techniques were applied. Cerebral radionecrosis after radiation therapy for scalp cancer has been reported in 17 cases between 1930 and 1978.[34] The complications were related to single high-dose treatment (2300 to 3000 cGy), high daily fractions (ie, more than 300 cGy per fraction), high dose (7500 cGy or more), or repeated courses of treatment. Ten of 12 patients operated on for brain necrosis were said to be cured. Soft tissue necrosis may occur, particularly after successful treatment of large lesions, but it is uncommon in our experience.

Parotid Area Irradiation

No evidence of permanent damage to the normal facial nerve has occurred in patients treated with radiation therapy alone, despite doses as high as 8000 to 9000 cGy in some instances. One patient had a transient nerve palsy that subsided in 4 months. Other potential complications include trismus, hearing loss, serous otitis media, perforation of the tympanic membrane, localized areas of necrosis, and bone exposure in the external auditory canal.

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26

MELANOMA OF THE HEAD AND NECK

ANDREW HARWOOD, SCOTT P. STRINGER, AND RODNEY R. MILLION

Melanoma's a dangerous nevus
Once in a while it'll peeve us
For if Clark says it's deep
Then it's time we should weep
On a bet that it likely won't leave us.

Captain Dale Curmanski

Melanoma primarily arising in the head and neck is a relatively uncommon problem, even for the physician dealing specifically with head and neck oncology. Particular emphasis is given here to the distinction of lentigo maligna (LM) and lentigo maligna melanoma (LMM) from the other forms of melanoma, and to the role of radiation therapy in the management of this disease. This is principally because these two areas have been neglected in the literature concerning melanomas of the head and neck. The chapter is divided into two parts: the first dealing with cutaneous melanoma, and the second with mucosal melanoma. Skin and mucosal melanomas are completely different in clinical appearance, treatment, and prognosis.

Ocular and conjunctival melanomas usually are considered specifically in ophthalmologic practice and are not discussed here. They are frequently managed by radiation therapy with a good rate of success, however, which is in keeping with the observations on the response of skin and mucosal melanoma.

CUTANEOUS MELANOMA

Incidence, Epidemiology, and Etiology

Melanoma represents about 3% of all types of cancer in North America. The overall incidence is about four cases per 100,000 population per year in the United States and Canada.[44] Melanoma of the head and neck accounts for 20% to 35% of all cases of cutaneous melanoma. The incidence of melanoma seems to be slowly rising. It commonly occurs between the ages of 30 and 60 years, with the exception of LM and LMM, which occur in the group 60 to 80 years of age and older.[22] It is extremely uncommon in children. Melanoma predominantly occurs in whites and is uncommon in the head and neck region in blacks and Asians. Strong evidence implicates exposure to sunlight in the pathogenesis of the melanoma, since it is particularly common in people with white skin living close to the equator, where the duration of exposure to sunlight is more prolonged. Melanoma of the skin most commonly occurs in people who tolerate the sun poorly, particularly those who freckle, burn easily, and do not tan readily. The other known factor of importance in the etiology of melanoma is genetic. First-degree blood relatives of a patient with melanoma are 1.7 times more likely to develop cutaneous melanoma than members of the general population. It is estimated that about 11% of melanomas may be hereditary. In familial cases of melanoma, a greater tendency exists for multiple melanomas to occur (an average of about three tumors per person). Clark and coworkers[12] have described an autosomal dominant B-K mole syndrome. Patients with this syndrome have multiple pigmented moles on the skin and a high incidence of transformation of these moles into malignant melanomas.

It is important for the clinician to recognize the hereditary form of malignant melanoma through careful patient follow-up for further primary melanomas and screening of blood relatives. This particularly applies to patients with the B-K mole syndrome.

Pathology and Patterns of Spread

Basically, three types of cutaneous melanoma in the head and neck occur.[10,11] Treatment and prognosis are vitally dependent on an understanding of the differences

between these three types: (1) LM; (2) superficial spreading melanoma (SSM); and (3) nodular melanoma (NM), including new lesions and those arising in a preexisting SSM or in a preexisting LM (LMM). Clinical appearance, pathologic features, prognosis, and treatment for each type are summarized in Table 26-1.

NM arising as a new lesion has a 30% to 50% metastatic rate; arising in preexisting SSM, 30%; and arising in a preexisting LM, 10%. LM and SSM most commonly grow slowly by peripheral or centrifugal enlargement. This is called the *radial growth phase*, and may last for many years in LM. Metastases rarely develop in a melanoma that is in the radial growth phase alone. The potential for metastases is markedly enhanced when the primary melanoma penetrates the deeper levels of the dermis. This is termed the *vertical growth phase*. The two methods of histologically staging melanoma recognize the importance of distinguishing these two growth patterns (see section on methods of diagnosis and staging).[8,10]

Lentigo Maligna and Lentigo Maligna Melanoma

Synonyms include Hutchinson's melanotic freckle,[37] circumscribed precancerous melanosis of Dubreuilh,[23] benign melanoma, and senile freckle.[2] The clinical and pathologic features of this condition are summarized in Table 26-1. Since LM is confined to the epidermis, it is a precancerous lesion. Characteristically, it is a slow-growing, pigmented lesion on the skin of the head and neck of an elderly person[30] (Fig. 26-1). The most common sites are the cheek (60% to 70% of cases), ear, and nose. It rarely occurs in the hair-bearing scalp and is uncommon outside of the head and neck, although it does occur on the penis and extremities. Commonly, there is associated solar damage to the skin. It represents about 10% of all cutaneous melanomas of the head and neck. If left untreated, LM will slowly increase in size over a 5- to 10-year period and may reach up to 5 to 10 cm in diameter. About one third to one half will develop invasion of the dermis (LMM),[58] ultimately, clinically manifested by a palpable nodule within the LM that may ulcerate and bleed. Microscopic dermal invasion in the larger LM (5 cm) can occur before the clinical development of a palpable nodule. Wayte and Helwig[58] have suggested that the older and the larger the LM, the greater is the risk of the development of NM.

The clinical features of LMM are summarized in Table 26-1. These include the development of a palpable nodule, which may ulcerate and bleed, within or at the edge of a preexisting LM (Fig. 26-2). The biologic aggressiveness of an NM arising in a preexisting LM is low, with a 10% or less chance of developing metastatic disease to the regional lymph nodes and distant sites. In the Toronto experience, with more than 30 patients with LMM, only one patient has developed distant metastases, and none has died of melanoma. This experience is similar to that of others.

The average time to onset of dermal invasion in an LM is 10 to 14 years.[2] Pathologically, LM and LMM are as distinctive microscopically as clinically. Severe solar damage frequently is present in the affected skin. One observes linear proliferation of atypical melanocytes in the basal region of the epidermis, and this may extend into the external root sheaths of hair follicles. The presence of a dense lymphocytic infiltrate also is common. When dermal invasion by the atypical melanocytes is present, the lesion is classified as a LMM. It is relatively uncommon to observe advanced vertical growth phase (ie, extension to Clark level IV or V) in an NM arising in a preexisting LM.

Superficial Spreading Melanoma

Superficial spreading melanoma accounts for 70% of all cutaneous melanomas and is intermediate in terms of biologic aggressiveness between LM and NM arising as a new lesion (see Table 26-1). Its peak incidence is in the fifth decade. As in LMM, both radial and vertical growth phases occur. The radial growth phase is shorter than in LM; the time to development of the vertical growth phase ranges from 1 to 2 years. The radial growth phase is associated with a metastatic potential of about 5% to

Figure 26-1. Lentigo maligna. (Harwood AR. Conventional fractionated radiation therapy for 51 patients with lentigo maligna and lentigo maligna melanoma. Int J Radiat Oncol Biol Phys 1983;9:1020. Copyright © 1983, Pergamon Press, Ltd.)

TABLE 26-1. Clinical History, Appearance, Histologic Features, Differential Diagnosis, Prognosis, and Treatment for Cutaneous Melanoma of the Head and Neck

	LM	LMM	SSM	NM
CLINICAL HISTORY	Slow growth of pigmented lesion, commonly on face of elderly person in sun-damaged skin	Development of nodule in preexisting LM that may have been present for many years; dermal invasion may occur before the development of a palpable nodule	More rapid growth than LM; does not grow as large as LM; palpable edge	Rapid growth of nodule, usually pigmented, in previously normal skin or preexisting nevus; bleeding or discharge may occur from a sore that will not heal; itching or other paresthesias may occur
APPEARANCE	No palpable nodule; from a few millimeters up to 10 cm in size; varying degrees of pigmentation, black and brown; white areas of regression may be present; edge impalpable, irregular, and serpiginous	The same as LM with the presence of a palpable nodule which may be ulcerated	Variety of color combinations (brown, black, blue, gray, white); scaly, crusted surface; skin furrows lost; irregular outline; nodules may be present and ulcerated; surrounding red flare may be present	Nodular growth; variable colors from black to red to white; erythema of skin at periphery; satellites in surrounding skin
DIFFERENTIAL DIAGNOSIS	SSM; pigmented basal cell carcinoma; pigmented actinic or seborrheic keratosis; nevus	See LM; NM developing previously untreated or in a preexisting SSM	Same as LM and LMM	Pigmented basal cell carcinoma; squamous cell carcinoma
PROGNOSIS	One third to one half ultimately develop dermal invasion (LMM)	10% develop regional metastases; distant metastases uncommon	20% to 30% develop metastases to regional lymph nodes; distant metastases are relatively common; risk of metastases rises with increasing penetration of dermis (Clark level) and thickness of lesion (Breslow thickness)	30% to 50% develop metastases to regional lymph nodes and distant sites; risk of metastatic spread rises with increasing penetration of dermis (Clark level) and thickness of lesion (Breslow thickness)
HISTOLOGIC FEATURES	Combination of severe solar degeneration of skin and linear proliferation of atypical melanocytes confined to epidermis	Similar to LM, but atypical melanocytes will have penetrated into the dermis	Proliferating melanocytes that invade the epidermis in a pagetoid fashion; dermal invasion nearly always present; invasive nodule may be composed of spindle or epithelioid cells	Downward growth of malignant melanocytes into dermis with minimal or no epidermal invasion
TREATMENT	Excision with 1–2 cm margins of normal skin; conventional fractionated irradiation	Excision of primary lesion is treatment of choice; conventional radiation therapy should be considered in certain cases	Excision of primary lesion is treatment of choice; conventional radiation therapy should be considered in certain cases	Wide excision of primary lesion; role of prophylactic lymph node dissection in selected cases is controversial; local excision and irradiation indicated in selected cases

LM, lentigo maligna; LMM, lentigo maligna melanoma; SSM, superficial spreading melanoma; NM, nodular melanoma.

Figure 26-2. Lentigo maligna melanoma.

10%. Once the vertical growth phase develops, about 30% will develop metastases to regional lymph nodes or distant sites.

Clinically, SSM grows more rapidly than LM, and it rarely grows to the same size as LM. It has a palpable edge with an irregular outline, but it is more circumscribed than LM (Fig. 26-3). A variety of color combinations of brown, black, and blue may be present, frequently with white areas of spontaneous regression. It has a scaly, crusted surface, and the skin furrows may be lost. Nodules may be present and ulcerated. The vertical growth phase usually appears by the time the lesion is 1 to 2 cm in size. The radial growth phase is characterized histologically by proliferating melanocytes that invade the epidermis in a pagetoid fashion. Microscopic invasion of the papillary dermis frequently is observed. The vertical growth phase is characterized by deeper penetration of the dermis by malignant melanocytes associated with nodule formation.

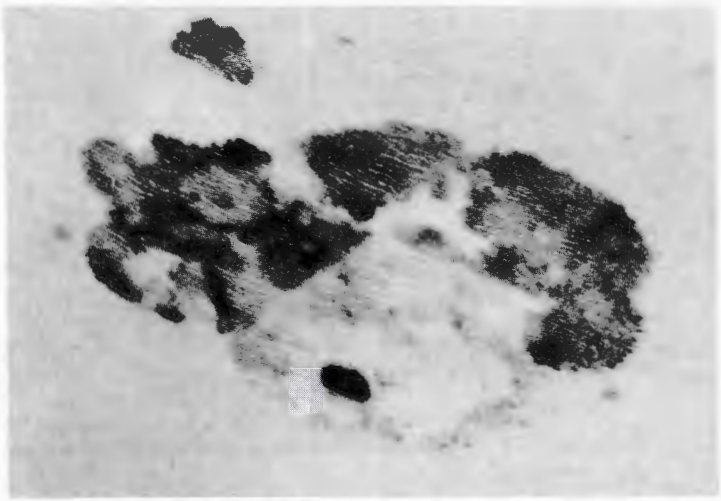

Figure 26-3. Superficial spreading melanoma.

Nodular Melanoma

Nodular melanoma arising as a new lesion is the most malignant form of the three varieties of cutaneous melanoma (see Table 26-1). Metastatic potential is about 50%. This type of NM is composed exclusively of a vertical growth phase, with malignant melanocytes invading into the deeper levels of the dermis. The host cellular response (eg, lymphocyte infiltration) is variable, but less than in LMM or SSM.[43]

Clinically, the lesion begins as a pigmented nodule in previously normal skin or in a preexisting nevus (Fig. 26-4). Growth is rapid, and ulceration and bleeding frequently occur. NM occasionally does not possess black or blue pigment and has the appearance of a reddish, nodular skin lesion; this amelanotic melanoma can resemble basal cell or squamous cell carcinoma and can be difficult to diagnose both clinically and pathologically. The most common sites are the face (50%) and neck (20%), followed by the ear and scalp.[17] Pathologically, no radial growth phase is observed in NM arising as a new lesion, and the lesion consists of malignant melanocytes in a nodule invading the dermis.

Distant Metastases

Lentigo maligna does not produce distant metastases. LMM develops distant metastases only after regional metastases have appeared, and even then the risk is small. Distant metastasis occurs in less than 5% of SSM. NM commonly develops distant metastases, and they may occur without spread to the regional lymph nodes, although the incidence increases if lymph node metastases are present. The time to appearance of distant metastases usually is within 1 to 2 years of diagnosis, but they have been observed to appear capriciously up to 20 years or longer after primary therapy.

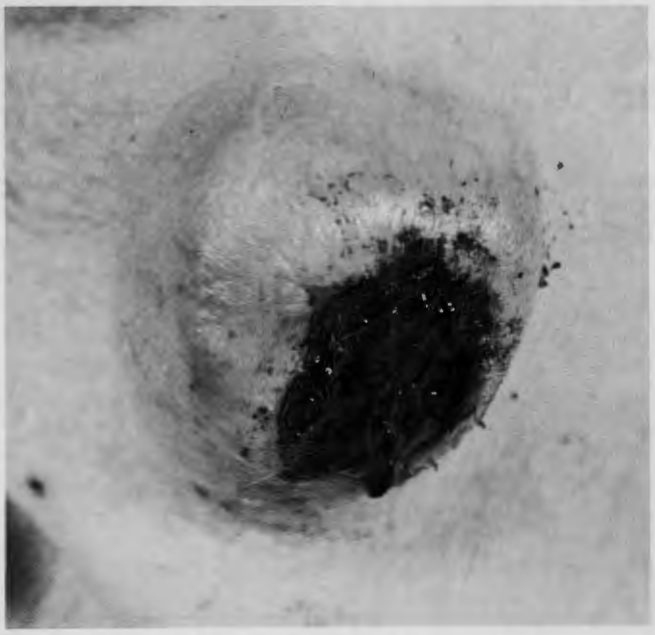

Figure 26-4. Nodular melanoma.

TABLE 26-2. Staging Procedures for Lentigo Maligna, Lentigo Maligna Melanoma, and Superficial Spreading Melanoma in Radial Growth Phase

Procedure	Rationale
Physical examination	To assess extent of radial growth phase, presence of vertical growth phase (ie, nodule formation), and presence of regional lymph node metastases, in order to determine adequate treatment margins
Biopsy	
Edge of lesion	To establish diagnosis and assess whether dermal invasion is present and extent of radial growth phase, in order to determine adequate treatment margins
Any palpable nodule	To establish whether dermal invasion is present and, if it is, to assess Clark level of penetration and Breslow thickness
Metastatic workup*	Not indicated unless lymph node metastasis is present or unexpected finding of Clark >3 or Breslow ≥0.75

* See Table 26-3.

Methods of Diagnosis and Staging

The diagnosis is established by either incisional or excisional biopsy. An excisional biopsy frequently is not possible in LM; the edge of the lesion should undergo biopsy, as well as any palpable nodule. The staging procedures for LM, LMM, and SSM in the radial growth phase are shown in Table 26-2. A full metastatic workup is not indicated in view of the low incidence of distant metastasis. This should be done only in the case that is behaving locally in an aggressive manner or has metastasized to the regional lymph nodes. The biopsy of any palpable nodule is important, since it allows assessment of the presence or absence of invasion of the dermis and the level of penetration if the dermis is involved. Two parameters of pathologic microstaging of the primary lesion have been shown to be important in determining prognosis in melanoma: (1) Clark level of penetration of the dermis,[10] and (2) Breslow thickness.[8]

Clark levels of penetration of the dermis are as follows[10]:

Level I: All tumor cells confined to the epidermis with no invasion of the basement membrane into the dermis (ie, melanoma in situ; eg, LM)

Level II: Tumor cells penetrating the basement membrane into the papillary dermis, but not extending to the reticular dermis

Level III: Tumor cells filling the papillary dermis and abutting, but not invading, the reticular dermis

Level IV: Tumor cells invading into the reticular dermis

Level V: Invasion into the subcutaneous tissues

The Breslow thickness method[8] involves measuring the maximum thickness of the primary melanoma using an ocular micrometer. Both the Clark and the Breslow methods of microstaging the primary melanoma are of prognostic importance (see section on treatment results). Correct assessment of Clark level and Breslow thickness clearly requires careful attention to biopsy technique and proper pathologic sectioning of the specimen. The staging procedures for an NM arising as a new lesion or in an SSM are shown in Table 26-3. Since distant metastasis is frequent in this form of melanoma, a limited metastatic workup is indicated. Chest roentgenography and whole-lung tomography or computed tomography (CT) scanning have the highest detection rate for occult metastatic disease. In view of the low detection rate, liver and bone scanning is not done routinely, unless an indication appears on clinical assessment or biochemical investigation that bone or liver metastases may be present.[57] A chest CT scan can be extended easily to include the liver for little additional expense and no added risk; liver CT scan is more sensitive than radionuclide images for the detection of hepatic metastases. Single photon emission computed tomography gallium studies are useful for detecting subclinical lymph node metastases and otherwise undetectable pulmonary metastases in patients with advanced Clark and Breslow levels.

A variety of clinical staging systems are used, distinguishing melanomas confined to the primary site, those with lymph node metastases, and those with distant metastases. When a lymph node dissection has been undertaken, a record of the number of nodes involved, size of nodal involvement, and presence or absence of penetration of the lymph node capsule is of prognostic importance, and these parameters should be determined by the examining pathologist. The 1988 American Joint Committee on Cancer pathologic staging system is listed below[1]:

Primary Tumor

pTX: Primary tumor cannot be assessed
pT0: No evidence of primary tumor
pTis: Melanoma *in situ* (atypical melanocytic hyperplasia, severe melanocytic dysplasia), not an invasive lesion (Clark's level I)
pT1: Tumor 0.75 mm or less in thickness and invades the papillary dermis (Clark's level II)
pT2: Tumor more than 0.75 mm but not more than 1.5 mm in thickness or invades to papillary–reticular dermal interface (Clark's level III)
pT3: Tumor more than 1.5 mm but not more than 4 mm in thickness or invades the reticular dermis (Clark's level IV)
pT3a: Tumor more than 1.5 mm but not more than 3 mm in thickness
pT3b: Tumor more than 3 mm but not more than 4 mm in thickness
pT4: Tumor more than 4 mm in thickness or invades the subcutaneous tissue (Clark's level V) or satellites within 2 cm of the primary tumor
pT4a: Tumor more than 4 mm in thickness or invades the subcutaneous tissue
pT4b: Satellites within 2 cm of the primary tumor

Regional Lymph Nodes

NX: Regional lymph nodes cannot be assessed
N0: No regional lymph node metastasis
N1: Metastasis 3 cm or less in greatest dimension in any regional lymph nodes
N2: Metastasis more than 3 cm in greatest dimension in any regional lymph nodes or in-transit metastasis
N2a: Metastasis more than 3 cm in greatest dimension in any regional lymph nodes
N2b: In-transit metastasis
N2c: Both (N2a and N2b)

Distant Metastasis

MX: Presence of distant metastasis cannot be assessed
M0: No distant metastasis
M1: Distant metastasis

TABLE 26-3. Staging Procedures for Nodular Melanoma Arising as a New Lesion or in a Superficial Spreading Melanoma

Procedure	Rationole
Physical examination	To assess extent of local disease (satellites), presence of lymph node metastases, and presence of distant metastases
Biopsy (excisional, if possible)	To assess Clark level of penetration of the dermis and Breslow thickness of the lesion
Metastatic workup: mandatory	
Peripheral blood hematologic and biochemical study (alkaline phosphatase, serum glutamic oxaloacetic transaminase, lactic dehydrogenase)	To assess presence of possible bone marrow, liver, or bone metastases
Chest roentgenogram and chest CT scan	To assess presence of lung metastases; chest CT scan may be extended to include screening of the liver
Metastatic workup: optional	
Brain CT scan	Done only if central nervous system symptoms are present
Liver CT scan	Done if there is hepatomegaly or elevated alkaline phosphatase or serum glutamic oxaloacetic transaminase levels
Bone scan	Done if bone pain is present or bony alkaline phosphatase level is elevated
Gallium scan	May detect subclinical lymph node metastases

CT, computed tomography.

M1a: Metastasis in skin or subcutaneous tissue or lymph nodes beyond the regional lymph nodes
M1b: Visceral metastasis

Stage Grouping

Stage I:	pT1, N0, M0
	pT2, N0, M0
Stage II:	pT3, N0, M0
Stage III:	pT4, N0, M0
	Any pT, N1 or N2, M0
Stage IV:	Any pT, any N, M1

Treatment

In view of the major and sometimes capricious differences in biologic behavior for LM and LMM, SSM, and NM arising as a new lesion or in a preexisting SSM, the treatment of these three entities is considered separately.

Lentigo Maligna and Lentigo Maligna Melanoma

In North America, the traditional method of treatment of LM and LMM has been by surgical removal,[7,14,18] although in continental Europe radiation therapy frequently has been employed.[4,20,45] LM or LMM is predominantly a disease of the skin on the face of elderly people. The lesion frequently reaches a large size before diagnosis. Surgical excision of such a large area of skin requires skin grafting to repair the defect; the cosmetic blemish created by the resection of a large LM, particularly on elderly, surgically unsuitable patients, has led to trying other treatment techniques, including 5-fluorouracil cream, cryotherapy, and electrodesiccation and cautery.[42,52] These methods have met with varying degrees of success. In the experience at the Princess Margaret Hospital, Toronto, with more than 40 cases, irradiation has proved to be a simple, well-tolerated, outpatient treatment that produces an excellent cosmetic result, superior to that produced by excision and full-thickness skin grafting (Table 26-4). This is illustrated in Figure 26-5, in which a patient with a large LM is shown before and after radiation therapy; and in Figure 26-6, which shows a similar patient before and after surgical treatment, including repair with a full-thickness skin graft. Considering the favorable experience with conventional irradiation at the Princess Margaret Hospital, the following management policy for LM and LMM is recommended:

1. Small LM or LMM on the free skin of the face should be primarily excised, provided this can be accomplished without a major resection requiring skin graft for reconstruction.
2. Small LM or LMM in sites where excision may produce cosmetic or functional deficits (eg, ear, eyelid, nose) should be treated primarily with fractionated irradiation, reserving surgery for patients (fewer than 10%) who have recurrent disease.
3. Large LM or LMM should be treated with conventional fractionated irradiation, reserving surgery for failure of irradiation to control the disease.

SURGERY. Surgery has been the traditional treatment for this disease, and the majority of patients have been cured. In view of the relatively benign nature of this type of melanoma, wide excision (ie, 5 cm border of normal tissue) is not routinely required. It has generally been conceded that a margin of 1 to 2 cm of normal skin around the lesion constitutes an adequate margin of resection.[7,14] Skin grafting is not routinely required unless the defect created is too large for coverage by advancement of flaps. Lymph node dissection is not indicated, unless clinically positive malignant nodes are present in the neck.

RADIATION THERAPY. Irradiation using the Miescher technique has been used for many years in Europe.[4,20,45] This technique involves the use of superficial irradiation using a contact therapy machine (10 to 20 KeV, 50% depth dose 1 mm) and the application of extremely high doses of irradiation (2000 cGy per treatment once weekly for five to six treatments).[45] The results achieved by several authors on more than 100 patients show a recurrence rate of less than 5%.[4,20,45] The major disadvantage with this technique is that the penetration of the x-ray beam is extremely limited and the fall-off of radiation dose is rapid. If, therefore, the lesion is only slightly thicker than appreciated on clinical examination (eg, with undetected but marked microscopic extension into the dermis), then the deeper portion of the tumor will be undertreated and subcutaneous recurrence will develop. This is probably the reason why the experience of Kopf and coworkers[40] with this technique was less favorable, with several recurrences consisting of invasive melanoma seen in the subcutaneous tissue. It is well recognized, particularly in the larger LM, that unrecognized microscopic invasion of the dermis can occur in the absence of a palpable nodule.

In Toronto, fractionated orthovoltage radiation therapy (100 to 250 KeV) was employed for many years.[16,29,30] The most commonly used fractionation regimens were 3250 cGy in 5 fractions over 1 week for LM smaller than 2 cm in size, 4500 cGy in 10 fractions over 2 weeks for LM 2 to 5 cm in size, and 5000 cGy in 15 fractions over 3 weeks

TABLE 26-4. Results of Radiation Therapy in the First 40 Cases of Lentigo Maligna and Lentigo Maligna Melanoma

Tumor Type	Patients	Controlled (Follow-Up)	Comment
Lentigo maligna	17	15 (6 mo–13 y)	Two local failures controlled by further irradiation and surgery
Lentigo maligna melanoma	23	21 (6 mo–7 y)	Two local failures both controlled by further surgery; one regional failure controlled by surgery and adjuvant irradiation

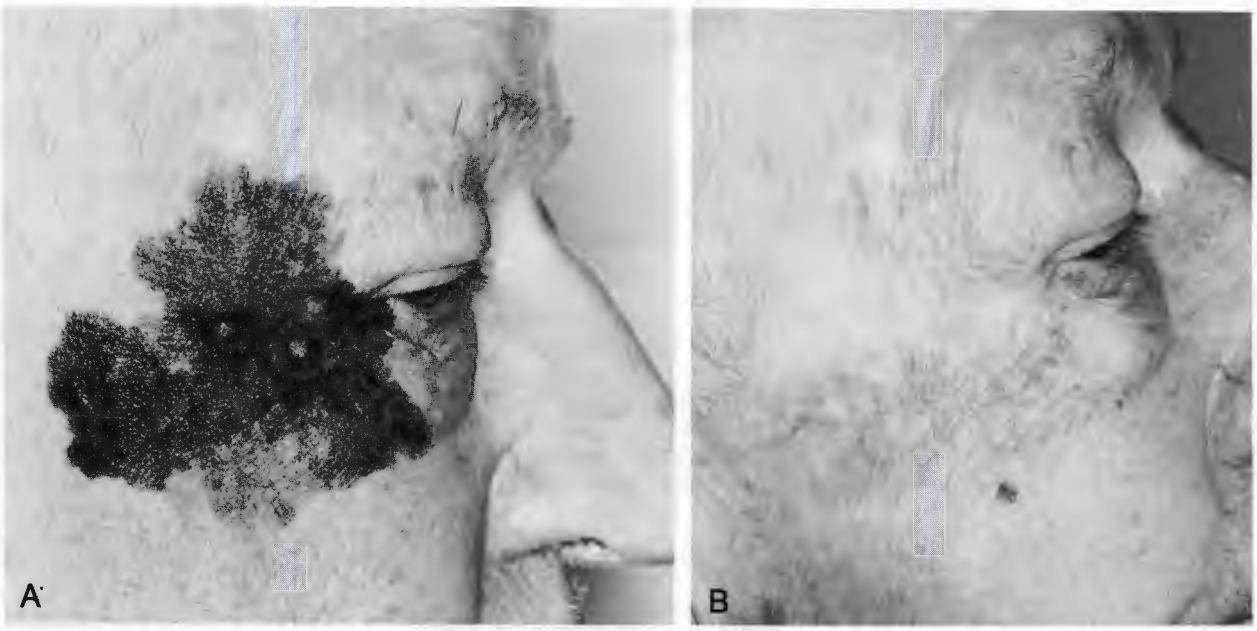

Figure 26-5. Large lentigo maligna just lateral to the eye. (*A*) Appearance before treatment. (*B*) Appearance after radiation therapy.

for large LM, such as illustrated in Figure 26-1. The method of irradiation used avoided the problem of possible undertreatment of unappreciated deep extension, since the penetration of even the most superficial x-ray beam that we have used (100 KeV) results in a 50% depth dose at 6 mm. Generally, a margin of 1 to 2 cm of normal skin was treated around the clinically obvious LM[30] (see Fig. 26-1). More penetrating irradiation (175 to 250 KeV) was used on thicker LMM (more than 0.7 mm thick). The results of treatment of more than 40 patients with fractionated irradiation are summarized in Table 26-5.[29] Thirty-eight of the 40 patients had lesions of the head and neck. Two LM patients developed recurrence after irradiation. One patient was 92 years of age when referred for treatment and refused fractionated irradiation. She was treated with a single exposure of 2000 cGy. The lesion faded and then regrew; 2½ years after the irradiation, the recurrence was excised, and the patient remained free of disease. The other patient received radiation therapy with an inadequate margin of normal tis-

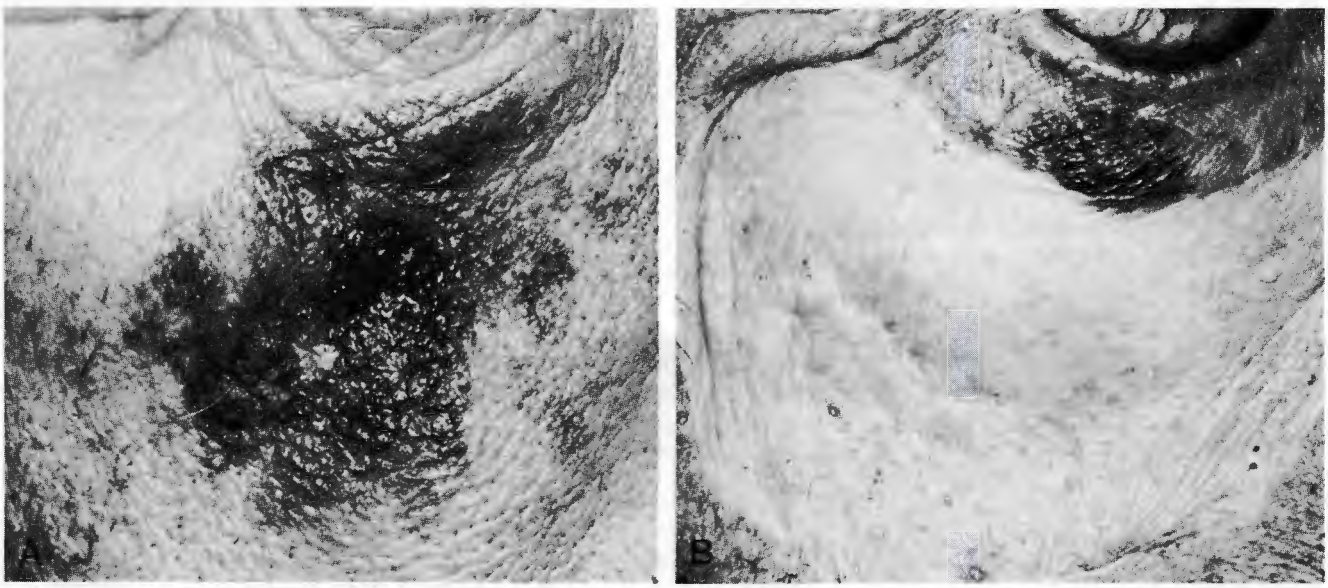

Figure 26-6. Lentigo maligna beneath the right lower eyelid. (*A*) Appearance before treatment. (*B*) Appearance after surgical treatment. Repair was a full-thickness skin graft. Note persistent disease in lower lid.

TABLE 26-5. Results of Radiation Therapy for Superficial Spreading Melanoma of the Head and Neck

Site	Clark Level	Age/Sex	Previous Treatment	Radiation Therapy	Result
Ear	3	54/M	Biopsy	4500 cGy/10 fractions/2 wk	NED 3 y
Cheek	3	78/F	Biopsy	4500 cGy/10 fractions/2 wk	NED 3 y
Cheek	2	55/F	Local excision, margins involved	4500 cGy/10 fractions/2 wk	NED 3 y
Eyebrow	2	27/F	Local excision, margins involved	5000 cGy/10 fractions/2 wk	Dead at 1 y*
Scalp	3	46/M	Recurrent after surgery	5000 cGy/10 fractions/2 wk	NED 5 y

NED, no evidence of disease.
* Local control; patient died of distant metastases.

sue, developed an edge recurrence, was treated again, and was alive and well 13 years after treatment of the recurrence.

Two LMM patients developed local recurrence after irradiation, and salvage was achieved with subsequent surgery. One regional lymph node recurrence occurred in a patient with a level V NM arising in an LMM on an ear. The primary lesion was controlled with conventional irradiation, but regional recurrence developed 18 months after primary treatment; neck dissection was carried out, followed by postoperative irradiation, since tumor was penetrating the lymph node capsule. The patient remained free of local and regional disease. To date, no deaths have occurred from melanoma in this group of patients. *Characteristically, the lesion may take up to 24 months (median, 9 months) to completely regress after irradiation*. The cosmetic results of irradiation were, in general, excellent. A representative example is given in Figure 26-5. No major complications of irradiation occurred in this group of patients; all patients developed an acute fibrinous irradiation reaction in the area of treatment that soon healed.

Superficial Spreading Melanoma

Excision remains the treatment of choice for SSM of the head and neck; however, radiation therapy should be considered as primary treatment when a contraindication to surgery exists, owing to medical reasons, or for locations where it is not feasible to do an adequate excision.

SURGERY. The principle of wide surgical excision for melanomas has been advocated for more than 70 years, and was based on pathologic studies of the frequency of dermal lymphatic permeation into the surrounding skin.[44] Generally, surgeons have advocated full-thickness excision of the skin with margins of 3 to 4 cm in all directions around the lesion. Such a philosophy, however, presents problems in the head and neck region where, owing to anatomic considerations, such wide excision is not always feasible. Recently, the necessity for such wide excisions has been questioned, particularly for SSM without the vertical growth phase or SSM with a vertical growth phase measuring less than 0.76 mm.[8] Breslow studied 62 melanomas less than 0.76 mm thick that were treated with a variety of resection margins varying from 0.1 to 5.0 cm. In these "thin" melanomas, no difference in local recurrence rates was found between patients with margins less than 0.5 cm wide compared with those with margins greater than 3.0 cm. Although this was a retrospective analysis and no prospective study has been done on this point, it seems reasonable to recommend for patients with SSM in the radial growth phase, particularly in the head and neck, that more limited resection with a margin of normal tissue both clinically and pathologically in the range of 0.5 to 1.5 cm is adequate.[19] In many cases, this will allow primary closure without the necessity for skin grafting. Where doubt exists as to the adequacy of the margins of the excision, postoperative irradiation can be applied as an alternative to further wide excision (see section on nodular melanoma).

The incidence of lymph node metastases in SSM in the radial growth phase is 5% to 10%. Elective lymph node dissection usually is not indicated.

RADIATION THERAPY. Little information exists in the English language literature[31] on the use of primary radiation therapy for SSM. Only five patients have been treated in Toronto for SSM of the head and neck by radical radiation therapy (see Table 26-5). In all five patients, the disease was locally controlled by irradiation; one patient died of distant metastases without local recurrence. Consideration should be given to the use of conventional fractionated irradiation for patients with SSM of the head and neck when positive or close margins exist after excision, or when conventional excision with an adequate margin cannot be carried out owing to anatomic considerations, age, or medical condition.

Nodular Melanoma

Nodular melanoma arising as a new lesion, or in an SSM, is the most virulent form of cutaneous melanoma of the head and neck, and is the area in which controversy about management is most marked.

Surgery is recommended as the treatment of choice for NM of the head and neck region. Two large surgical series report an overall survival rate of 25% at 5 years, with 50% to 60% of stage I patients and 12% to 30% of stage II patients alive at 5 years.[6,13] Little information exists in the literature specifically on the curative use of irradiation in NM. The experience at the Princess Margaret Hospital[33] suggests that local excision followed by high-dose irradiation is an option that deserves further study. Generally, we recommend wide local excision of the primary lesion. Local excision plus high-dose irradiation is applied when conventional surgical therapy is not believed to be appropriate because of the medical condition of the patient, or because the location of the primary lesion makes wide excision impossible or too mutilating.[33]

Elective neck dissection is a controversial issue. Some

studies conclude that it does not improve survival,[53] and some studies show a significant survival advantage.[5]

Some patients are cured when operated on for clinically palpable lymph node metastases, and therefore, removal of subclinical disease should produce even better results. Elective neck dissection is considered at the University of Florida (Gainesville) for melanomas 1.5 cm thick (0.75 mm thick in high-risk areas such as the scalp and neck) and for ulcerated or nodular lesions. Elective neck dissection is also recommended when follow-up will be inadequate. Irradiation is given for unresectable melanoma in lymph nodes (either primary or recurrent) and is used after lymph node dissection in patients with a high risk of recurrence in the neck. Adjuvant chemotherapy or immunotherapy is not used unless patients are participating in a clinical trial.

SURGERY. Surgical resection of the primary lesion or lymph nodes has been accepted, and in the majority of reports, represents the sole treatment for NM of the head and neck for the last 70 years.[6,13,22,48,50,56] With respect to the primary lesion, wide excision with a 3- to 5-cm cuff of normal skin around the lesion has been recommended where feasible. Some centers have been recommending less aggressive surgical excisions for lesions thinner than 0.76 mm in maximum vertical height. In this situation, a number of centers have shown that local excision with a 0.5- to 1.0-cm margin of normal tissue around the lesion is adequate and associated with a low local recurrence rate.

For the thicker lesions (Breslow thickness more than 0.75 mm, or Clark level IV or V), wide excision is still recommended as standard treatment (minimum 2.5- to 5.0-cm margin where anatomically feasible in the neck and scalp).[56] Lesions of the ear and nose are frequently treated by amputation. With such radical excisions, the local recurrence rate is 4% to 15%, although the cosmetic defects produced may be substantial.[6,56] In a series by Storm and coworkers,[56] all patients referred with local recurrences were found on assessment of the initial pathology report to have had an inadequate excision with a margin of less than 2.5 cm. Whether the defect should be covered by primary closure, rotation of flaps, or split-thickness skin grafting depends more on local factors than on any sense that a particular method of reconstruction results in a higher recurrence rate.[6] Generally, wide excisions on the nose, scalp, or forehead require split-thickness skin grafts for closure.[6]

When palpable lymph nodes are present, the generally accepted method of treatment is neck dissection. Frequently, in addition to dissecting the neck contents on the side involved, a superficial parotidectomy and dissection of the lymph nodes of the parotid area are carried out, particularly when the primary lesion is on the forehead, temple, cheek, or ear (see Chap. 25 for management of parotid area lymph nodes). A posterolateral lymph node dissection is frequently carried out for primary lesions on the posterior skin of the ear and the posterior scalp[6] (see Chap. 6 for posterior lateral neck dissection). We are studying the use of adjuvant radiation therapy after surgical dissection of lymph nodes for certain high-risk patients. The survival after radical neck dissection for patients with gross melanoma in regional neck nodes is poor, however, with 5% to 30% surviving 5 years.[6,13,50]

For patients with a clinically negative neck, a general consensus exists that the following groups of patients should not have elective lymph node dissection: patients with NM arising in a preexisting LM; those with thin NM (less than 0.76 mm) arising as a new lesion or in an SSM; and elderly patients, or those in poor general condition.[6]

Elective lymph node dissection is considered for patients with NM, arising as a new lesion or in an SSM, and level III or greater.

RADIATION THERAPY. It has been repeatedly stated in the literature that NM is a radioresistant tumor.[38] Rarely, however, are data provided to justify such an opinion. A detailed historical review of the radiosensitivity of NM showed that, generally, reports quoting radioresistance of melanoma are based on limited experience with orthovoltage irradiation used only when the disease was far advanced and unsuitable for surgery.[31] In Toronto, Richards treated NM by local excision followed by high-dose postoperative irradiation (5000 cGy in 10 fractions over 2 weeks). The results of Richards' work were analyzed by Dickson in 1958.[21] Of 121 patients treated by local excision and irradiation, 41% were alive and well at 5 years, a result comparable with that achieved by wide local excision during the same period. In contrast, 71 patients treated by local excisions alone had a 20% 5-year survival rate. The reason for this success was probably two-fold. First, he was treating a series of patients probably similar to those submitted to surgery rather than a carefully chosen, unfavorable group of recurrent or palliative cases. Second, by pure chance, Richards was using large doses of radiation per fraction. As a result of Dickson and Richards' work, a limited number of patients with NM have been treated by the technique described by Dickson.[21]

A substantial amount of work has been done on the radiobiology of melanoma in recent years to determine if it is, indeed, an intrinsically radioresistant tumor.[31] Studies on experimental melanoma lines in cell culture and on human melanoma cell lines grown *in vitro* indicate that the melanoma cell is not intrinsically radioresistant, but that melanoma cells have a large capacity to repair sublethal radiation damage. This indicates that to overcome this effect, large doses per fraction are necessary (270 cGy or more). Our own clinical experience, in addition to that of others, supports this contention.[27,31,35,49] It is apparent that major differences exist in radiosensitivity between different melanomas, since some response is even observed to 200-cGy daily fractions.[15] Also, some evidence suggests that hypoxia may be present in melanomas; and substantial evidence indicates that in some cases, melanoma may be slow to regress after irradiation, further contributing to the impression of radioresistance.[31]

Only one randomized, prospective study has been carried out on 56 patients with positive pathologic findings for the lymph nodes, to test whether postoperative irradiation of the neck improves survival for melanoma of the head and neck.[15] The dissected neck received 5000 cGy in 28 fractions with a 3- to 4-week split after 2500 cGy. Three of 27 irradiated patients developed recurrence in the treatment field. Only one recurrence occurred in 29 patients treated with neck dissection alone. No survival benefit was seen in the adjuvant irradiation group.

As a result of the historical experience of Dickson and Richards, 16 patients with NM of the head and neck were

treated with a technique of incisional (14 patients) or excisional (two patients) biopsy followed by high-dose postoperative irradiation as an alternative to wide excision.[31,33] The results are summarized in Table 26-6. Fourteen of the 16 patients had local control of disease, and 6 of the 14 were alive and well from 2 to 14 years after irradiation.

Another 16 patients were treated with irradiation for locally or regionally recurrent disease after unsuccessful surgery. In contrast to the primary cases, only 2 of the 16 patients with recurrence achieved local–regional control with irradiation, and in three additional patients salvage after irradiation failure was achieved with further surgery. Ten patients died of melanoma and one died of intercurrent disease with no melanoma.

Analysis of local control versus irradiation fraction size revealed that local control was 71% if a dose of greater than 400 cGy per fraction was used, compared with 25% if less than 400 cGy per fraction was used.

The data in the primary cases treated by the Dickson technique indicate that this method of treatment is worthy of further study in NM of the head and neck. We continue to use the technique of local excision followed by high-dose postoperative irradiation in selected patients in whom, due to age or medical condition or the location of the primary lesion, the more traditional wide local excision is too hazardous or would result in a poorer cosmetic result.

The results of irradiation for recurrent melanoma of the head and neck were less favorable; however, surgical therapy also is relatively ineffective in this situation.[6] Only when recurrence of the primary lesion alone occurs can salvage by surgery be achieved in a significant proportion of cases. In our patients with recurrent melanoma of the head and neck treated by irradiation, we only had three such patients, one of whom had salvage by irradiation.

The disadvantage of the Dickson technique is that it can only be applied to relatively small volumes of tissue (skin and subcutaneous tissue) and is, therefore, only suitable for treatment of primary disease.[31] *When disease occurs in lymph node–bearing areas, large volumes of tissue must be treated, and the Dickson fractionation regimen is greater than the radiation tolerance for normal tissue.* As a result of this and the belief that large dose-per-fraction irradiation provided higher response rates in melanoma, a fractionation regimen employing an 800-cGy tumor dose as a single dose given on three occasions on day 0, 7, and 21 was initiated in 1975.[39] This *day 0, 7, 21* regimen is useful for treatment of large volumes, such as the entire neck, but again, it is not applicable for systemic metastases in brain, lung, or liver where such radiation doses are above the limits of normal tissue tolerance, although limited volumes of these organs occasionally may be treated in this fashion. *Care also has to be taken with this regimen, since it is above spinal cord tolerance, and generally the dose to the spinal cord is limited to a maximum of two fractions of 800 cGy.*

TABLE 26-6. Results of Radiation Therapy for Nodular Melanoma of the Head and Neck

Results	Patients
No evidence of disease (2–14 y)	6
Local failure, dead of melanoma	2
Local control, dead of melanoma: regional and distant	2
Distant only	3
Dead of intercurrent disease, no melanoma	3
Total patients with no local recurrence	14
Total patients treated	16

Three clinical subtypes of disease have been treated[39]: (1) microscopic residual melanoma after surgery (generally after lymph node dissection); (2) gross residual melanoma (large volume) after surgery; and (3) recurrent melanoma.

The first group consisted of 22 patients who were referred for treatment after complete surgical excision, but who were considered to be at high risk for microscopic residual tumor and subsequent development of recurrence in the surgical field. This group included patients who, on pathologic assessment of the specimen, had a tumor penetrating through the lymph node capsule, multiple nodes involved in the specimen, or one node greater than 3 cm in size with complete destruction of the node by melanoma. Eighteen of the 22 patients so treated have had no recurrence in the irradiated volume to date (12 to 50 months after irradiation) and 10 are alive and well (12 to 50 months after irradiation). The four in-field recurrences all occurred within 15 months of irradiation, and two patients died less than 7 months after irradiation with an extremely aggressive form of melanoma that was unresponsive to therapy. The eight patients who died despite local–regional control of their disease died of metastatic melanoma (six in less than 15 months after irradiation). This illustrates the highly aggressive nature of some melanomas and emphasizes the need for effective systemic therapy in this group of patients. The results suggested that large dose-per-fraction irradiation reduced the recurrence rate in the surgical field, and randomized prospective studies to test this are indicated.

Thirty-two patients were treated with day 0, 7, 21 radiation therapy for gross residual or recurrent unresectable melanoma. Twelve (38%) had complete remission of frequently massive disease, and seven are alive and well up to 56 months after irradiation. Only two patients had progression of disease within the treated volume within 3 months of irradiation. The response rate is higher than we have previously observed with conventional irradiation, although a randomized comparison has not been done.

Morbidity rate of the treatment has been low, provided that care is taken to limit the maximum given dose to 825 cGy per fraction to avoid excessive fibrosis.[39] We continue to use this fractionation regimen in melanomas of the head and neck for gross residual or unresectable (principally nodal) recurrent melanoma when a large volume (more than 5 cm of skin and subcutaneous tissue) must be irradiated. It offers good palliation with a much higher complete response rate than achieved by any chemotherapeutic combination in use. It is well tolerated, and survival may be prolonged in some patients. Ang and coauthors[3] reported the preliminary experience of adjuvant radiation therapy for 83 patients with melanoma of the head and neck treated at M.D. Anderson Hospital (Houston) from 1983 to 1988. Group 1 consisted of 35 patients presenting with lesions 1.5 mm thick or Clark's level III, but without clinically positive adenopa-

thy. They received elective irradiation to the tumor bed and ipsilateral lymphatics: 600 cGy per fraction, two fractions per week to a total dose of 3000 cGy. The spinal cord dose was limited to 2400 cGy. Twenty-eight patients remained alive and disease free; one developed local–regional recurrence, one had nodal and visceral recurrence, and five relapsed with distant metastasis alone. Follow-up ranged from 2 to 58 months (median, 15 months). The 2-year probability of local–regional control was 95%, and the 2-year probability of survival was 80%.

Group 2 consisted of 15 patients presenting with stage II disease (ie, nodal involvement). They were treated with an operation combined with preoperative or postoperative irradiation. When the irradiation was given preoperatively, the treatment consisted of 2400 cGy in four fractions over 2 weeks, and when it was given postoperatively, it consisted of 3000 cGy in five fractions over 2½ weeks. No patients developed distant metastasis alone, and one patient developed widespread subcutaneous metastases (one of which was within the irradiated fields). The 2-year probability of local–regional control was 90%, and the 2-year probability of survival was 71%.

Group 3 consisted of 33 patients with previously excised primary lesions presenting with nodal relapses, but without distant metastases. Preoperative or postoperative irradiation (administered as in group 2) was combined with a limited nodal dissection. Twenty-one patients had no evidence of disease after a median follow-up of 16 months (range, 2 to 60 months or more). One patient developed in-field recurrence alone, three patients had local or regional recurrences and distant metastasis, and eight patients developed distant metastases alone. The 2-year probabilities of local–regional control and survival were 83% and 69%, respectively.

The authors presented surgery-alone data for comparison and concluded that irradiation reduced the local and regional recurrence rate.

Irradiation often is useful for palliation of distant metastases to brain, bone, and other tissues.

CHEMOTHERAPY AND IMMUNOTHERAPY. A detailed review of chemotherapy for metastatic melanoma is outside the scope of this review and has been published elsewhere.[44] Dacarbazine is the most active single agent in melanoma, with response rates on the order of 20% being observed. The complete response rate is 5% or less, significantly poorer than for day 0, 7, 21 irradiation applied to localized masses.

Little specific information is available on the use of adjuvant immunotherapy for malignant melanomas of the head and neck, with the exception of one report of 25 patients treated with adjuvant BCG (bacille Calmette-Guérin) for melanoma of the head and neck with lymph node metastases.[24] Results were compared with those of 17 nonrandomized, concurrent patients with metastases to the neck nodes. Survival benefit was shown in favor of patients receiving adjuvant immunotherapy. This benefit has not yet been confirmed in other centers. A number of major randomized studies have been carried out in both the United States and Canada testing the value of immunotherapy in cutaneous melanoma. Conclusive data supporting improved survival with adjuvant immunotherapy are lacking. Adjuvant immunotherapy or chemotherapy, therefore, cannot be recommended for use in melanoma of the head and neck unless carried out as part of a prospective randomized clinical trial.

Treatment Results

The type of melanoma is a factor of major prognostic importance: With LM the cure rate is, essentially, 100%; with LMM, the 5-year survival rate is 95% or better; and with SSM, the 5-year survival rate is 90% to 95%. The 5-year survival rate for NM arising as a new lesion is about 50%, however, and that for NM arising in SSM is 75%.

Since the prognosis for LM and SSM is so favorable, the majority of series analyzing prognostic factors have limited further analysis to NM arising as a new lesion or in SSM.[13,22,25,44,59] In NM, prognostic factors of importance include clinical stage and pathologic microstaging of the primary lesion. When the disease is confined to the primary lesion, the 5-year survival rate is 50% to 75%; with metastases to regional lymph nodes, 5-year survival rate is 5% to 30%; and with distant metastases, no 5-year survival occurs. The results are shown by Clark level and Breslow thickness in Table 26-7. Women have a better prognosis than men[25] (by 10% to 20% at 5 years). Patients with scalp or ear melanomas have a poorer prognosis than patients with face melanomas.[25] The more intense the lymphocyte infiltration, the better is the prognosis.[25] Within clinical stage II (lymph node metastases), involvement of more than four nodes, penetration of the lymph node capsule, and node size greater than 5 cm are associated with a poor prognosis.[39,59]

Balch and coauthors[5] analyzed 1786 clinical stage I melanomas treated at the University of Alabama, Birmingham, and the University of Sydney, Australia. The addition of elective neck dissection gave a significantly improved 10-year survival rate compared with wide local excision alone for lesions 0.76 to 3.99 mm deep (Table 26-8).

Byers[9] reviewed results for modified elective neck dissection, and at 5 years found a 10% recurrence rate for the neck when clinically negative and 14% when clinically positive.

Ballantyne,[6] in a retrospective series of stage IA patients (no palpable lymph nodes, disease confined to the primary site, not recurrent), analyzed 115 patients who did not have an elective lymph node dissection and 75 who did. The reasons for selection of treatment were not given. Twenty-seven (23%) of 115 patients who did not

TABLE 26-7. Results of Treatment According to Pathologic Microstaging (Clinical Stage I)

Pathologic Microstaging	5-Y Survival (%)	With Lymph Node Metastases (%)
Clark level		
1	100	0
2	94	6–10
3	76	29–33
4	69	32–43
5	57	33–63
Breslow thickness (mm)		
<0.7	95	ND
0.7–1.5	72	ND
≥1.5	53	ND

ND, no data.

TABLE 26-8. Clinical Stage I Melanoma: Wide Local Excision Versus Wide Local Excision Plus Elective Radical Neck Dissection—10-Year Survival*

	University of Alabama		University of Sydney	
	0.76–1.49 mm	1.5–3.99 mm	0.76–1.49 mm	1.5–3.99 mm
WLE	43%	20%	65%	45%
WLE + radical neck dissection	82%	67%	87%	70%

WLE, wide local excision.
* Data from Balch and associates.[5]

have an elective lymph node dissection subsequently required therapeutic neck dissection. Overall survival rate for this group was 61%. Of 73 patients who underwent elective lymph node dissection, 11 (15%) had positive findings for nodes; overall survival rate for this group was 77% at 5 years. Differences in survival were due to a lower incidence of distant metastases in the elective dissection group (22% versus 31%) and a lower incidence of primary recurrence (5% versus 9%).

Olson and coworkers[48] found no difference in survival rate between patients receiving elective neck dissection and those who did not. Of particular interest in the Olson study was that skip involvement of nodes was not encountered; if proximal nodes did not contain tumor, more distal nodes also gave negative results. The incidence of nodes with occult melanoma in the Olson series was 23%. When melanoma was found in three or more nodes in the operative specimen, prognosis was extremely poor (less than 20%). Others have found that once melanoma has metastasized to regional lymph nodes, this is strongly predictive of the presence of disseminated disease.[25,50]

MUCOSAL MELANOMA

Mucosal melanomas of the head and neck represent 0.5% to 2.0% of all malignant melanomas.[46] A review of the literature in 1969 indicated 195 reported cases of mucosal melanoma of the nose and paranasal sinuses.[36] The most common location within the head and neck is the nasal cavity, where melanomas represent 13% to 18% of all malignant tumors.[41,55] In contrast, Lederman[41] reported only 10 melanomas (6%) in 172 ethmoid tumors and only one primary melanoma (0.3%) in 356 antral tumors. The Toronto experience is similar, with melanomas representing 14% of all malignant nasal cavity tumors and 2% of all malignant maxillary antral tumors. Melanomas arising in other sites within the head and neck region are rare, with only isolated cases being reported. A 2:1 male-to-female incidence ratio exists, and the majority of cases occur in the sixth and seventh decades.[51]

The disease rarely occurs in blacks, although pigmentation of the oral mucosa is common in black Africans.[51] The reason why mucosal melanoma is predominantly a disease of white North Americans is unclear. Melanoma of the oral cavity is more common among the Japanese and frequently associated with melanosis. An associated mucosal melanosis is seen less frequently in mucosal melanomas arising in whites.

Pathology

Gross appearance of the tumor is variable. It is commonly a solid, polypoid growth. The color may be white to pink, red, gray, brown, or black. The median diameter of the lesion at the time of diagnosis is 1.5 cm.[36] Microscopically, the lesions also are variable. They generally consist of solid growths of medium-sized cells with large nuclei. In contrast to cutaneous melanomas, lymphocyte infiltration rarely is seen. Melanoma pigment is readily identified with special staining (Fontana stain) in two thirds of specimens. In one third of cases, persistent searching for melanosomes is required, including the use of electron microscopic examination. About one third of malignant melanomas arising in the nasal cavity are amelanotic. In view of the major differences in treatment and prognosis between mucosal melanoma and other anaplastic malignant tumors of the nasal cavity and paranasal sinuses, it is important for pathologists to consider melanoma in the differential diagnosis. The correct diagnosis was missed initially in two cases in our series, and inappropriate treatment was prescribed.

Patterns of Spread

Local extension is common and may be extensive, with bone destruction and extension from the nasal cavity into the paranasal sinuses; local patterns of spread are similar to the carcinomas of these regions (see Chap. 22 for a full discussion of the anatomy and patterns of spread). Nodal disease is present in 10% to 23% of patients when first seen.[28,51] Subsequent development of regional lymph node metastases in the absence of local recurrence or disseminated disease is uncommon, occurring in less than 5%.[51] Nodal disease may appear at some time in the course of the disease in up to 25% of patients, although this is most common in association with local recurrence and distant metastases.[28,54] Hence, regional lymph node metastasis in most series has not presented a significant problem in management, and in few patients did the lymph node metastases, per se, contribute to death.[54] Distant spread to liver, lungs, brain, and subcutaneous tissues is common, and is the major cause of death. Five percent to 10% of patients have distant metastases at presentation, and the vast majority of patients with this disease ultimately die of distant metastases.[51] A continual attrition rate from distant metastases occurs more than 5 years after treatment, and little evidence exists to suggest that this disease can be cured.[26,36]

Clinical Picture

The clinical picture clearly depends on the site of origin of the melanoma within the head and neck. Nasal melanomas present with the same symptoms as other nasal tumors: bleeding, obstruction, and discharge.[36,54] A typical case is shown in Figure 26-7. Anterior rhinoscopy usually reveals a solid submucosal mass that may be polypoid and that bleeds easily. About 50% of cases are obviously pigmented on clinical assessment. Extensive disease with extension into the sinuses with associated bone destruction is common. Lymph node and distant metastases may be present when patients are first examined. It is extremely uncommon to see an associated nevus in a melanoma of the nasal cavity. Symptoms may have been present up to 2 years, and it is common for patients to have had previous nasal polypectomies.[36]

In the oral cavity, the primary tumor is frequently associated with intraoral melanosis, and the lesion may be large, covering an extensive portion of the oral cavity before diagnosis.[54] Ulceration and bleeding are the most common symptoms of oral cavity melanoma; significant pain rarely occurs.[54]

Figure 26-7. Patient presented with nasal bleeding. Anterior rhinoscopy revealed an area of black melanosis on the nasal septum. Biopsy revealed nodular melanoma. The patient was treated with day 0, 7, 21 radiation therapy and went into complete remission for 1 year; a local recurrence developed, which was excised. She was alive and well 2 years later.

Methods of Diagnosis and Staging

The diagnosis of oral cavity melanoma is relatively easy, considering its typical appearance and frequent association with melanosis. Nasal cavity melanoma can be difficult to diagnose in about one third to one half of cases, owing to clinical lack of pigmentation in one half of cases, and absence of melanosomes under light microscopic study in one third of cases pathologically.

A deep wedge scalpel biopsy should be made to permit accurate assessment of the degree of thickness and penetration of the primary lesion. When difficulty is encountered in trying to visualize melanosomes under light microscopic study, electron microscopic examination is beneficial to establish the diagnosis. The deep biopsy also permits accurate assessment of the degree of thickness and penetration of the primary lesion.

A summary of staging procedures is essentially the same as shown for cutaneous melanoma (see Table 26-3) with the exception of pathologic microstaging, which is of little known benefit in mucosal melanomas. The size of the lesion also is of limited benefit in predicting prognosis. Because the vast majority of patients with this disease die of it, irrespective of extent of disease, the need for an extensive staging system is not great. Imaging may be used, depending on the site of origin. For instance, it is almost always employed in sinonasal lesions. Most series confine themselves to a simple clinical staging system in which stage I indicates disease confined to the primary site; stage II, primary lesion plus lymph node metastases; and stage III, distant metastases.

Treatment

We have undertaken a detailed review of the literature on the treatment of this form of melanoma with particular attention to the relative roles of surgery and irradiation.[32] A review of the literature up to 1969 revealed an 11% 5-year survival rate and only one patient (1%) surviving 10 years.[36] Similarly, a large series of 56 patients from the Mayo Clinic (Rochester, MN) failed to show any evidence of cure in patients with mucosal melanoma.[26] Clearly, these data must influence treatment decisions, since treatment for this condition essentially is palliative, although the palliation may be prolonged (5 to 10 years in some cases).

Generally, the tumor has been stated to be radioresistant, but these observations have been based on the results in advanced cases.[28,32,36,47] My own experience, in addition to that of others who have used radiation therapy in earlier stage disease, clearly shows that the concept of radioresistance is incorrect. Since the most common site for mucosal melanomas of the head and neck is the nasal cavity and the results for primary radical surgery are equivalent to radical radiation therapy in equivalent-stagea patients, radiation therapy (day 0, 7, 21) is used as the initial treatment and extensive en bloc excision is reserved for those whose tumors fail to respond to irradiation, or who have recurrence after irradiation. It is difficult to justify major resections initially when the results are so poor; resection should be reserved for use only in patients for whom irradiation fails.

Surgery

Surgery has been the recommended primary method of management in most series.[26,28,36,47,54] Wide en bloc excision has been recommended for the primary lesion in the absence of regional or distant metastases. Elective lymph node dissection is not indicated, in view of the low incidence of subsequent development of lymph node metastases in the absence of local or distant recurrence, and the fact that the most common primary site is in the midline (nasal cavity). No evidence shows that extending the limits of excision has any influence on survival. The majority of long-term survivors with surgery also had irradiation.[32]

Therapeutic neck dissection is indicated for lymph node metastatic disease.

Radiation Therapy

A review of the literature on the irradiation of mucosal melanomas revealed only 24 reported cases (including 12 cases from Toronto: 7 nasal cavity, 3 oral cavity or oropharynx, and 2 antral tumors) that allow detailed review of the radiation parameters and outcome; these are individually reported in detail elsewhere.[32] The complete remission rate locally was 72% (18 of 25 areas treated, one patient being treated twice). Seven of the 18 patients who had complete local remission relapsed locally from 9 to 144 months after irradiation (median, 36 months). Eleven patients remained in complete remission locally from 9 to 54 months (median follow-up, 20 months). Five are alive and well (6 months to 3½ years); four died of intercurrent disease without melanoma; one developed an isolated regional recurrence, was treated surgically, and is alive and well; and one died of distant metastases with no local or regional disease.

Of seven patients whose tumors did not completely respond to irradiation, six died of melanoma and one is alive and well after surgery (this patient had a partial response and the residuum was excised). All patients with local recurrence after a complete remission died of melanoma. The results are summarized in Table 26-9.

In view of the risk of late relapse, none of the patients alive and well after radiation therapy can be considered cured. It is apparent that patients who respond to radiation therapy survive substantially longer than those who do not. Local control versus irradiation fraction size in the 25 areas treated is analyzed in Table 26-10. Follow-up is somewhat shorter in the large dose-per-fraction group, since this method of treatment has only been used in recent years. Although patient numbers are small, large dose-per-fraction irradiation seems to produce a greater chance of local control, as in cutaneous melanoma of the head and neck.

TABLE 26-9. Results of Radiation Therapy in Mucosal Melanoma of the Head and Neck (25 Patients)

Results	Patients
Incomplete remission (7 patients)	
Dead of melanoma	6
Salvaged by surgery	1
Complete remission (18 patients)	
Alive and well (6 mo–3½ y)	5
Local recurrence, dead of melanoma	7
Local control, regional or distant recurrence	2
Alive and well (1)	
Dead of melanoma (1)	
Dead of intercurrent disease, no melanoma	4

TABLE 26-10. Local Control in Mucosal Melanoma Versus Irradiation Fraction Size

Dose Per Fraction (cGy)	Controlled/Treated	Duration (mo)
0–399	5/18	9–54
≥400	6/7	6–42

Our own policy is to use the day 0, 7, 21 regimen discussed in the section on cutaneous melanoma. We have now treated seven mucosal melanomas with this fractionation regimen; it is well tolerated, and we have experienced *no major morbidity, provided that the spinal cord and brain are shielded for the third fraction or the dose to the spinal cord and brain does not exceed 500 to 600 cGy per fraction*. If patients do not achieve complete clinical and radiologic remission within 3 months of irradiation, then surgical excision is undertaken, provided that no evidence of distant metastases exists. This approach allows optimization of treatment so that some patients may achieve prolonged palliation without major resection. For those who relapse after irradiation and still have localized disease, the surgical option is still available.

The technique used for irradiation depends on the site (eg, nasal cavity, oral cavity) and extent of the lesion. For small nasal cavity melanomas, frequently a direct anterior electron field or high-energy x-ray field (20 to 25 MV) with appropriate bolus is used. For more extensive nasal cavity or sinus tumors, multiple-field techniques are used, generally employing a direct, high-energy x-ray beam (8 by 8 cm to 10 by 10 cm in size) with bolus and a cutout for the eye combined with two lateral wedged cobalt-60 fields (bull's-eye technique).[34] The neck is not irradiated.

Chemotherapy

Little information exists in the literature on chemotherapy in mucosal melanoma. Generally, mucosal melanomas respond more poorly to chemotherapy than cutaneous melanomas, and we have not seen a single complete remission with chemotherapy. Generally, dacarbazine or melphalan is tried.

Prognosis

As noted above, the prognosis for mucosal melanomas is extremely poor, and a constant attrition rate occurs with time, so that it cannot be considered a curable disease, although prolonged palliation can be obtained in some patients. In a review of the literature until 1969, Holdcraft and Gallagher[36] found an 11% 5-year survival rate and a 1% (one patient) 10-year survival rate. A report of 26 well-documented cases with a 5-year survival rate of 38% has been published.[54]

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27

MAJOR SALIVARY GLAND TUMORS

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Tumors of the parotid, submandibular, and sublingual glands account for 3% to 4% of all neoplasms of the head and neck. Radiation-induced neoplasms have been reported.[20] An increased risk of tumors of the major salivary gland may be associated with female breast cancer. The average age of patients with malignant neoplasms is 55 years, and for benign tumors, it is about 40 years. About one fourth of parotid tumors and one half of submandibular tumors are malignant. About 80% of all tumors of the major salivary gland occur in the parotid gland.

ANATOMY

Parotid Gland

The parotid ("around the ear") gland, the largest of the major salivary glands, is a relatively simple structure with rather complex and important anatomic relationships[7,30] (Figs. 27-1 and 27-2). The gland is shaped by the surrounding muscles, bones, vessels, and nerves that come in contact with it. It is roughly L shaped, with its superior border at the zygomatic arch. The anterior border, although variable, does not extend beyond the orifice of the parotid duct, which is located in the buccal mucosa opposite the second maxillary molar tooth. The inferior border is the upper border of the posterior belly of the digastric muscle. Superiorly, the gland lies adjacent to the anterior and inferior portions of the external auditory canal, and then extends to the tip of the mastoid. Deep to the anterior portion of the parotid gland are the masseter muscle and the horizontal ramus of the mandible. The retromandibular part of the gland extends between the horizontal ramus of the mandible and the mastoid tip. The deep portion is in relationship to the styloid process with its three attached muscles (the stylohyoid, styloglossus, and stylopharyngeus), the lateral process of C1, the internal pterygoid muscle, and the contents of the parapharyngeal space. The small superior portion of the parotid gland is tucked between the external auditory canal and the condyle.

That portion of the superficial lobe that lies between the angle of the mandible and the mastoid tip is referred to as the *tail* of the parotid; the tail, which represents about 20% of the total mass of the gland, measures about 2 cm in diameter and is 1 to 2 cm thick. In older, obese patients, the gland becomes infiltrated with fat, enlarges, and becomes more distinct to palpation; the tail of the parotid then may be confused with a lymph node or parotid mass. The fatty parotid tails usually are similar on both sides, which helps in making the diagnosis.

A number of accessory lobes have been reported in a variety of locations, particularly along Stensen's duct. Normal salivary gland tissues occasionally may be seen in lymph nodes.

Embedded within the gland are the facial nerve, filaments from the auriculotemporal nerve, part of the external carotid artery and its two terminal branches, the maxillary and superficial temporal arteries, the posterior facial vein, and a number of lymph nodules and nodes (see Fig. 27-1 and Chap. 6, Fig. 6-7).

The facial nerve courses through the parotid gland, and for this reason the surgeon artificially divides the parotid gland into a lateral (superficial) lobe and a medial (deep) lobe. No true fascial plane separates the two lobes. The lateral lobe accounts for 70% to 80% of the parotid gland. Little or no deep lobe exists lateral to the horizontal ramus of the mandible and masseter muscle, with most of the deep lobe occurring in the retromandibular portion of the gland (see Fig. 27-2). Anteriorly, the nerve lies near the undersurface of the gland, essentially on the surface of the masseter muscle.[14]

The parotid gland is encompassed by fascia that is sufficiently dense to contain most parotid infections and benign and low-grade malignant tumors until they be-

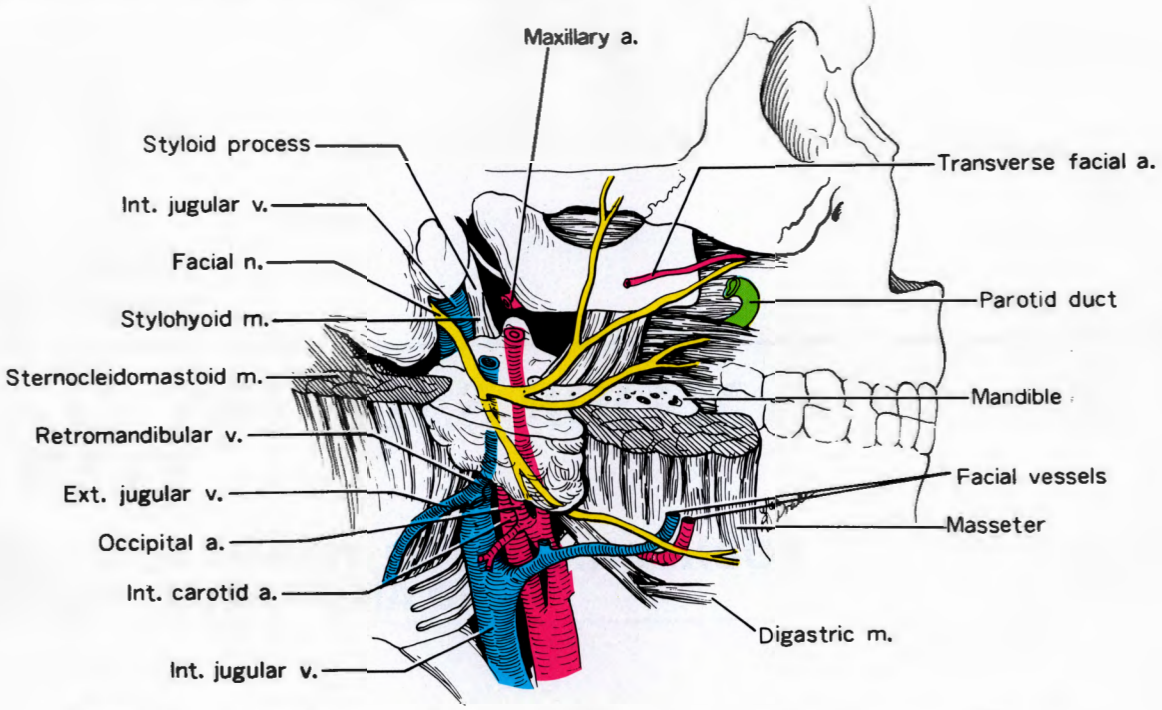

Figure 27-1. Regional anatomy of the parotid. (Note: Posterior facial vein is cut away.) The main trunk of the facial nerve divides into the superior branch, which is made up of the temporal, zygomatic, and buccal branches, and the inferior branch, which is made up of the marginal and cervical branches. (Redrawn from Beahrs OH, Adson MA. The surgical anatomy and technic of parotidectomy. Am J Surg 1958;95:887)

come massive. The superficial fascia overlying the gland usually is dense and connected by multiple fibrous septa that penetrate deeply into the glandular tissue.[39] The fascia between the parotid gland and the conchal and tragal cartilages, however, is thin; this is a weak spot through which tumor and infection may penetrate toward the ear canal. The fascia separating the deep lobe from the parapharyngeal space (stylomandibular fascial membrane) is thin, particularly in the upper and lower portion; therefore, tumors involving the deep lobe may produce a mass bulging into the posterolateral pharyngeal wall, tonsil, palate, and nasopharynx.

The facial nerve penetrates the parotid gland almost immediately (within 1 cm or less) on leaving the stylo-

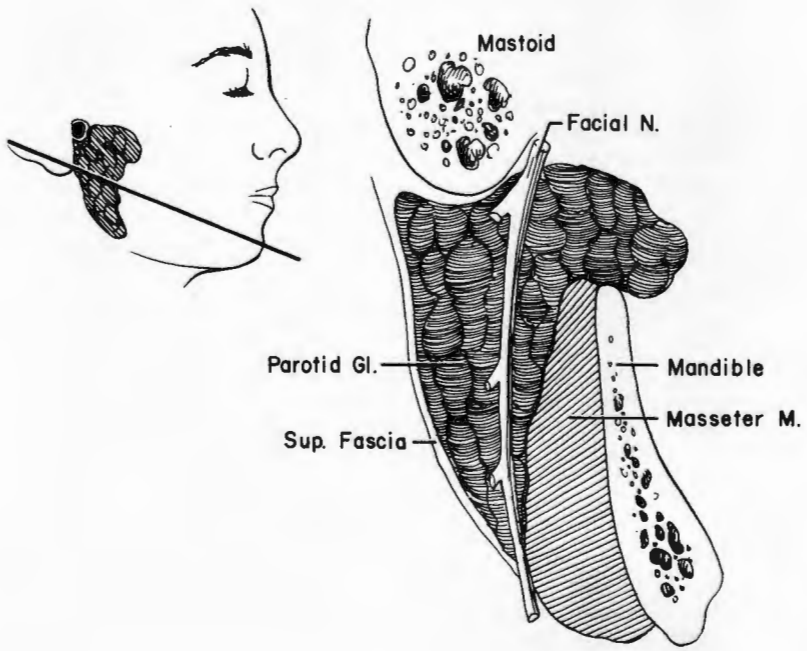

Figure 27-2. Relationships of the facial nerve to the parotid gland, mastoid, and masseter muscle.

mastoid foramen; it travels through a small fat pad on its course between the foramen and gland. Extensive anastomoses usually occur between the five major branches, but in 13% of cases, no anastomoses occur between the terminal nerve branches. Damage to these anastomotic branches does not necessarily produce significant facial weakness. Anastomoses are frequent between the terminal branches of the three temporofacial divisions, and less frequent between the two branches of the cervicofacial division. The auriculotemporal nerve, a branch of the trigeminal nerve, runs from the upper masticator space through the deep lobe of the gland, and gives branches that contain parasympathetic fibers to the gland. This nerve provides one route of perineural spread to the base of the skull and the intracranial contents. Severing of these branches may contribute to the development of Frey's syndrome (gustatory sweating).

The parotid gland is richly supplied from several arteries, which freely anastomose within the gland. The external carotid artery divides within the deep portion of the gland into the posterior auricular, superficial temporal, and maxillary arteries. Branches of the posterior auricular, external facial, transverse facial, and occipital arteries send branches to the gland.

The superficial temporal and maxillary veins combine within the gland to form the retromandibular vein (see Fig. 27-1). Both the retromandibular and posterior facial veins lie deep to the facial nerve. Branches of these veins may produce troublesome bleeding during parotidectomy or during a radical neck dissection when the tail of the parotid is transected.

The sensory nerve supply to the parotid skin and part of the pinna is by way of the greater auricular nerve (C2–3). This nerve is usually severed during parotidectomy, causing a permanent loss of sensation in the ear lobe, which may be disconcerting to patients who wear earrings. A portion of the greater auricular nerve may be used as a nerve graft to repair the facial nerve.

Lymphatics

The lymph nodes of the parotid area are shown in Figure 27-3 (see Chap. 6, Fig. 6-7). The superficial preauricular nodes, usually one or two in number, lie outside the fascia of the parotid gland and immediately in front of the tragus in the subcutaneous fat and in close relationship to the superficial temporal vessels. The nodes are typically less than 3 mm in size. These lymph nodes drain the skin of the ear, temple, and upper face, including the eye and the nose. They are most frequently involved by metastatic skin cancer (carcinoma and melanoma) and lymphoma, but not usually by parotid neoplasms. Secondary invasion of the gland and facial nerve may occur (see Chap. 25). The preauricular lymph nodes drain either to the superficial lymph nodes (inferior parotid lymph nodes) along the external jugular vein as it crosses the sternocleidomastoid muscle, or they may communicate directly with the internal jugular chain of lymph nodes.

The true parotid lymph nodes are composed of two groups within the fascia of the parotid gland. One group, lying within the substance of the parotid gland, is represented by numerous lymph follicles and four to ten small lymph nodes scattered along the retromandibular, posterior facial, and jugular veins. Thus, some of them lie deep to the facial nerve and may not be removed by lateral lobectomy. A second group lies between the gland and the superficial fascia. One or two nodes lie in front of the ear, and one or two between the inferior aspect of the tail

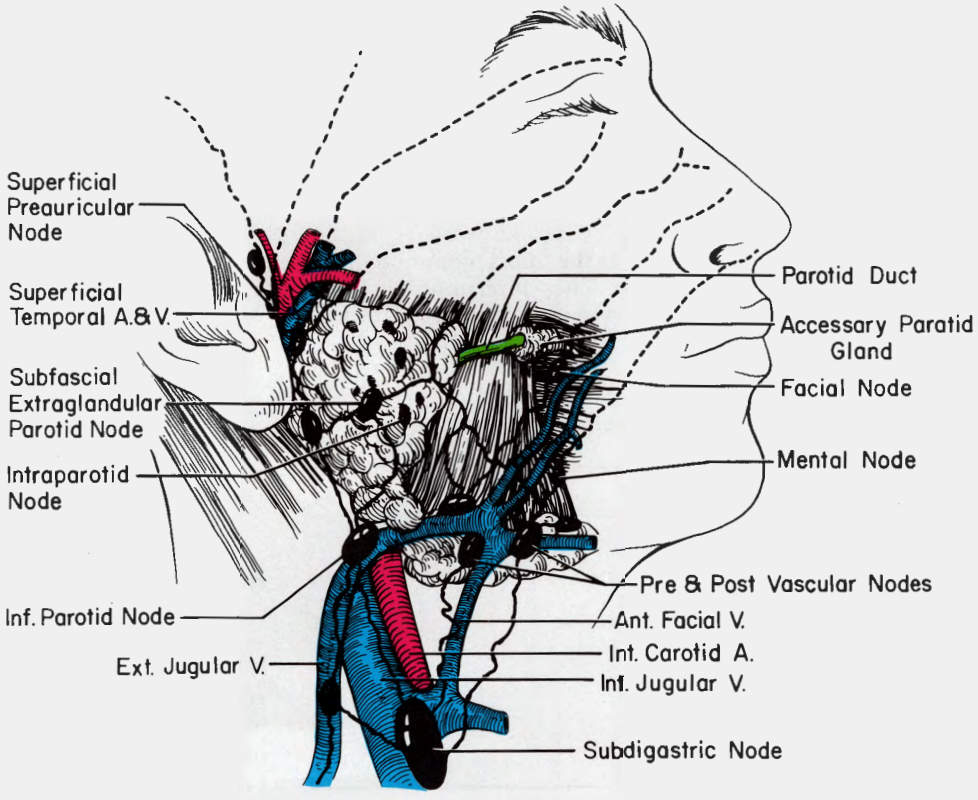

Figure 27-3. Parotid area lymphatics. The superficial preauricular and inferior parotid lymph nodes lie outside the fascia of the parotid gland. The parotid lymph nodes lie between the fascia and the lateral surface of the parotid. There are multiple intraparotid lymph nodules. (Modified from Conley JJ. Salivary glands and the facial nerve. New York, Grune & Stratton, 1975:12)

of the parotid and the anterior border of the sternocleidomastoid muscle, in association with the external jugular vein. These latter lymph nodes are referred to as the subparotid or tail-of-parotid lymph nodes. An enlarged subparotid node is difficult to distinguish from a mass originating in the tail of the parotid gland.

Submandibular and Sublingual Glands

For the anatomy of the submandibular and sublingual glands, see Chapter 16.

PATHOLOGY

A large variety of benign and malignant neoplasms occur in the major salivary glands. The approximate incidence rate of the various neoplasms in the parotid gland is given in Table 27-1. The initial diagnosis for parotid masses most often is made by frozen section at the time of exploration. It may be difficult to distinguish between benign and malignant neoplasms on frozen section, and patients must be advised of this possibility.[26]

Miller and coworkers[26] analyzed the accuracy of frozen-section diagnosis for 132 parotid lesions. The frozen-section diagnosis was the same as the final diagnosis in 110 cases (83%). Six cases (5%) were called benign on frozen section and were changed to malignant on final diagnosis. In three instances, the malignant portion of the tumor was not included in the sample taken for frozen section. Fifteen tumors were called malignant on frozen section, and none was changed to benign. A definitive diagnosis could not be given on frozen section in ten cases; four turned out to be malignant and six were benign. Variability and overlap occur in the microscopic appearance of this group of neoplasms. The clinical picture should be considered in determining the treatment plan. The appearance of the lesion on computed tomography (CT) or magnetic resonance imaging (MRI) usually will correlate with whether or not the mass is invasive.

Benign Tumors

Benign Mixed Tumors

Benign mixed tumors are the most common neoplasms of the salivary gland. They first appear in patients in their early 20s, with a mean age at presentation of 40 years. Benign mixed tumors may grow to an enormous size, but they usually are 2 to 7 cm in diameter. Consistency of the mass varies with the relative amount of connective tissue, cartilage, vascular stoma, and cystic degeneration. They are discrete, slow-growing neoplasms surrounded by an imperfect pseudocapsule that is traversed by fingers of tumor. Enucleation or removal with a narrow cuff of normal tissue results in recurrence in at least 20%.

The histologic distinction between benign and malignant mixed tumor is only occasionally difficult. Lesions considered benign for many years may unexpectedly become clearly malignant and develop metastases. Some benign mixed tumors recur innumerable times and display a locally aggressive behavior despite a benign histologic appearance.

TABLE 27-1. Relative Frequency of Parotid Neoplasms

Histologic Type	Incidence (%)
Benign mixed tumors	65
Miscellaneous benign tumors	15
Malignant mixed tumors	4
Mucoepidermoid carcinoma	6
Adenoid cystic carcinoma	3
Acinic cell carcinoma	3
Adenocarcinoma	3
Miscellaneous malignant tumors	1

Papillary Cystadenoma Lymphomatosum (Warthin's Tumor)

A benign tumor, usually 1 to 3 cm in diameter, papillary cystadenoma lymphomatosum probably arises from lymphoid elements. It accounts for 5% to 10% of all parotid neoplasms. The tumor is encased by a thin, but complete capsule. It occurs predominantly in the tail of the parotid in older men, is bilateral in about 10%, and may be multiple or extraglandular on one or both sides. Recurrences are rare after excision.

Benign Lymphoepithelial Lesions (Godwin's Tumor)

Benign lymphoepithelial lesions account for about 5% of benign lesions. The tumor may be bilateral and is more common in women. Excision may be followed by recurrence. Multiple, benign lymphoepithelial lesions have recently been recognized as a manifestation of human immunodeficiency virus (HIV) infection and may predate any other signs of acquired immunodeficiency syndrome.

Oncocytoma

Oncocytoma (oxyphiladenoma) usually is a benign, slow-growing tumor found mostly in an older age-group. The well-circumscribed, encapsulated tumor has a dark appearance reminiscent of melanoma. Case reports exist of low-grade malignant oncocytomas.

Basal Cell Adenoma

The basal cell adenoma is an uncommon benign lesion appearing in older people. It is histologically and clinically benign and is cured by simple excision. It must be distinguished from basal cell carcinoma of the skin metastatic to parotid lymph nodes.

Malignant Tumors

Low-Grade Malignancy

ACINIC CELL CARCINOMA. Acinic cell tumors typically are classified as slow-growing, low-grade neoplasms. They appear in all age-groups and are more common in women. Grossly, they may appear encapsulated, but microscopically some lesions invade contiguous

structures such as bone, nerve, skin, and blood vessels.[1,6] This neoplasm should not be considered benign. Batsakis and associates[6] collated ten series reported between the years 1954 and 1979. Ninety-four of 257 patients (37%) developed a local recurrence, and 15% developed metastasis. These tumors will recur (or a new acinic cell carcinoma will develop) after inadequate removal, sometimes as long as 25 to 30 years after initial treatment. Metastasis occurs in a significant percentage of cases; histologic grading is unreliable for predicting metastases.

MUCOEPIDERMOID CARCINOMA, LOW GRADE. The majority of mucoepidermoid carcinomas are low-grade, solid or cystic, slow-growing lesions that appear in any age-group. Little or no capsule exists, although they are well circumscribed and are readily cured by wide excision. A few tumors act aggressively and may widely infiltrate the normal gland or become fixed to the skin. The mucin produced by the neoplasm may incite inflammatory changes about the edge of the mass.

High-Grade Malignancy

MUCOEPIDERMOID CARCINOMA, HIGH GRADE. A few of the mucoepidermoid carcinomas behave in an aggressive fashion, widely infiltrating the salivary gland and producing lymph node and distant metastases. They may be difficult to distinguish histologically from a high-grade epidermoid carcinoma. Perineural invasion is infrequent, and late recurrences are uncommon.

ADENOCARCINOMA, POORLY DIFFERENTIATED CARCINOMA, ANAPLASTIC CARCINOMA, AND SQUAMOUS CELL CARCINOMA. These histologic types tend to appear late in life and have an aggressive behavior. True squamous cell carcinomas may arise from the salivary glands, or their ducts in rare cases[35]; almost all cases are either metastases to the preauricular or parotid lymph nodes from squamous cell carcinoma of the skin[10] or high-grade mucoepidermoid carcinomas that are producing scant amounts of mucin (see Chap. 25).

MALIGNANT MIXED TUMORS. Malignant mixed tumors account for 5% or less of all mixed tumors. Mixed tumors may be malignant when first diagnosed. A small percentage of benign mixed tumors probably progress to a frank malignancy and have an aggressive behavior. The malignant portion may be epithelial only, or all the components may appear malignant. It may be small and discrete or may dominate the mass to the point that recognizable benign mixed tumor elements are difficult to identify. The malignant portion usually is the epithelial component and may appear as an adenocarcinoma, epidermoid carcinoma, or undifferentiated carcinoma, or all types may coexist.

ADENOID CYSTIC CARCINOMA. The growth rate varies from slow to rapid. Metastases to regional lymph nodes and distant sites occur. Perineural involvement is a characteristic finding, and facial nerve palsy may be present at the time of diagnosis. Recurrences may appear many years after initial treatment in the slow-growing lesions. The high-grade lesions have a greater proportion of solid epithelial pattern on histologic examination.

SALIVARY DUCT CARCINOMA. Salivary duct carcinoma is a recently defined malignant tumor of major salivary glands with a microscopic pattern similar to mammary ductal carcinoma. It should be considered as a high-grade malignancy, with a 42% incidence of lymph node metastasis reported in one series.[2]

LYMPHOEPITHELIOMA (MALIGNANT LYMPHOEPITHELIAL LESION). Lymphoepithelioma is a rare carcinoma of the salivary gland occurring nearly always in the parotid gland of the mongoloid race, usually Eskimos and Chinese.[19]

PATTERNS OF SPREAD

Parotid Gland

Benign Mixed Tumors

Benign mixed tumors grow by expansion and local infiltration, and because of their slow growth, rarely cause facial nerve palsy, although the nerve may be severely stretched by large masses. When incompletely excised, multiple nodules of tumor develop within the surgical bed. The skin may become involved in recurrent lesions by implantation. Bone invasion rarely occurs; a large mass may cause pressure defects of adjacent bone.[29] A sudden increase in the growth rate may indicate a malignant change, although a few benign mixed tumors may intermittently grow rapidly. Facial nerve palsy is an almost certain sign of malignant change.

Malignant Tumors

The malignant neoplasms infiltrate the parotid gland, invade the facial nerve or the auriculotemporal nerve, and spread along nerve sheaths. Tumor may invade the adjacent skin, muscles, and bone. Adenoid cystic carcinoma, in particular, widely infiltrates all adjacent tissues without respect for anatomic planes. The external jugular vein may become thrombosed, and the external carotid artery may be narrowed by compression. Obstruction of the parotid duct rarely is seen. Deep-lobe tumors invade the parapharyngeal space and base of the skull and compromise cranial nerves.

The rate of lymph node metastasis varies with grade, size, T stage, and the salivary gland involved. Little difference in the rate of lymph node metastasis exists among the various high-grade histologic types; the risk increases with recurrent disease at the primary site.

Armstrong and associates[5] reviewed 474 previously untreated tumors of the major salivary gland. Sixteen percent of patients with parotid tumors and 8% of those with submandibular or sublingual tumors had clinically involved lymph nodes on admission. The rate of clinically and pathologically proven adenopathy was 2% for low-grade, 16% for intermediate-grade, and 34% for high-grade lesions. On elective neck dissection (90 patients) or regional node removal (13 patients), subclinical disease was discovered in 21% of submandibular cases and 9% of parotid cases. Patients with high-grade tumors had a 49% risk of subclinical disease compared with 7% for those with low- to intermediate-grade tumors. Analysis by T stage showed a 7% risk for T1 and T2 tumors, 16% for T3, and 24% for T4 tumors. Analysis by size revealed a 61% rate of subclinical disease for patients with tumors 4 cm or larger compared with 17% for those with tumors less than 4 cm.

In 304 patients, the neck was clinically free of tumor.

TABLE 27-2. Incidence of Lymph Node Metastases in Malignant Salivary and Mucous Gland Tumors (179 Patients)

Site	Malignant Tumors	Lymph Node Metastasis (%)
Parotid gland	66	24
Submandibular and sublingual glands	21	38
Oral cavity	31	29
Upper air passages*	40	10
Larynx and trachea	8	12
Pharynx	6	67
Esophagus	1	0
Lacrimal glands	6	17

* Including nasopharynx.

(Rafla-Demetrious S. Significance and treatment of lymph node metastases of malignant mucous and salivary gland tumors. Am J Roentgenol Radium Ther Nucl Med 1973;117:595)

These patients were only observed, and 8% eventually developed a neck recurrence.

Analysis of the distribution of involved nodes showed that a full functional neck dissection or complete ipsilateral neck irradiation would be needed to encompass all disease (ie, levels I to V) for both parotid and submandibular primaries (see Chap. 6).

The risk for lymph node metastasis by anatomic site for 179 malignant tumors of major and minor salivary glands is shown in Table 27-2.[31] About one half of the metastases were present at the time of first diagnosis.

Submandibular Gland

Malignant tumors that extend through the capsule of the submandibular gland fix the tumor to the adjacent mandible, invade the mylohyoid muscle and eventually the tongue and the lingual and hypoglossal nerves, and extend to the oral cavity. Skin invasion occurs in advanced cases. Obstruction of the submandibular duct is not a feature of malignant or benign tumors. Lymph node metastases occur in about 30% of patients (see previous section).

CLINICAL PICTURE

Parotid Gland

The great majority of patients with either benign or malignant tumors present with a solitary, painless mass that is easily seen and felt just in front of or just below the ear lobe. Mild, intermittent pain is associated with a few of the masses, but it does not reliably distinguish between benign and malignant lesions. A more pronounced pain more often is associated with malignant neoplasms or inflammatory conditions. Patients with benign mixed tumors and low-grade malignant tumors may have a history of the presence of a mass for many years with little or no observable growth, and then an increase in size is noticed that brings them to the physician. Facial nerve weakness is an infrequent presenting complaint (2% to 3%), but when present, it indicates malignancy. Tumors involving the deep lobe may produce dysphagia, sore throat, ear symptoms, headache, and rarely, cranial nerve palsy or trismus.

Occasionally patients will present with a slowly progressive facial palsy, which is at first regional and often associated with temporary periods of improvement. The paralysis eventually becomes complete and may be accompanied by mild pain. A complete investigation, or multiple investigations, fails to disclose a mass or cause. Conley and Selfe[13] reported 14 such cases in which a neoplasm eventually was discovered. The usual culprit was a malignant tumor or neurilemoma adjacent to the nerve in the deep lobe or isthmus. The diagnosis was made by exploration of the extraosseous main trunk of the nerve. Bell's palsy was the most common erroneous diagnosis. An earlier diagnosis should be possible today with modern imaging.

Physical Examination

The mobility of the mass depends on its size and location. Minimal to moderate fixation or reduced mobility may occur in both benign and malignant neoplasms and does not distinguish between the two. Tumors presenting in the deep lobe may bulge the palate and lateral pharyngeal wall. Deep lobe tumors may present as a retromandibular mass with little or no bulge into the oropharynx. Most lesions originating in the deep lobe are large at the time of diagnosis and present in both the oropharynx and the upper neck.

Salivary flow is not affected by either benign or malignant tumors. Advanced malignant lesions may affect the facial nerve. The mandibular branch of the trigeminal nerve may be involved when tumor tracks along the auriculotemporal nerve to the base of the skull; pain is an associated finding. More rarely, the glossopharyngeal, vagus, spinal accessory, and hypoglossal nerves and the sympathetic chain are affected if the poststyloid parapharyngeal space is invaded.

Tumor may become fixed to the skin or even ulcerate through to the surface.

Submandibular Gland

Both benign and malignant neoplasms present as a mass beneath the mandible. Mild pain occasionally is a feature, but does not distinguish between benign and malignant lesions. Moderate to severe pain usually indicates malignancy. Nerve deficits involving cranial nerves V, VII, and XII were diagnosed in 14% of patients with carcinomas.[37] The mass may be fixed, and skin invasion and eventually ulceration may occur. Clinically positive lymphadenopathy occurs in about one quarter of malignant cases.

Physical Examination

Bimanual examination is used to evaluate size, mobility, local extension of the mass, and the presence of stones in the duct. The tumor mass usually is tethered or fixed to the mandible, unless it is small. Loss of mobility occurs with both benign and malignant lesions. It is often difficult to distinguish between an enlarged submandibular gland involved with cancer and an enlarged,

fixed lymph node involved with cancer. The tumor may infiltrate the skin in malignant lesions. Cranial nerves V, VII, and XII should be evaluated.

METHOD OF DIAGNOSIS AND STAGING

Differential Diagnosis

Parotid Gland

It is often easy to distinguish nonneoplastic from neoplastic conditions by history, physical examination, and simple diagnostic tests. The distinction between benign and malignant neoplasms is more difficult unless obvious nerve palsy, pain, or metastatic cervical lymph nodes occur.

Gallia and Johnson[16] reviewed 140 patients who eventually underwent parotidectomy for diagnosis. Only 11% had malignant masses; the remainder had benign neoplasms (62%) or nonneoplastic conditions (27%).

Conditions that may be confused with a parotid tumor include the following:

- Metastatic cancer, lymphoma, or leukemia involving lymph nodes of the parotid area
- Reactive lymphadenopathy
- Fatty replacement, tail of parotid
- Chronic parotitis
- Sarcoidosis
- HIV infection
- Stone in duct
- Cysts (branchial cleft, dermoid)
- Hypertrophy associated with diabetes
- Hypertrophy of masseter muscle, unilateral or bilateral
- Neoplasms of the mandible
- Prominent transverse process of C1 (atlas)
- Penetrating foreign bodies
- Hemangioma or lymphangioma
- Lipoma

Submandibular Gland

The differential diagnosis of a submandibular mass centers around inflammatory disease, squamous cell carcinoma metastatic to a lymph node, and a primary neoplasm of the submandibular gland.

Episodic pain and mass are the hallmark of inflammatory disease, but about one third of the lesions will be asymptomatic.[16]

Obstructive sialoadenitis is a common cause of submandibular gland enlargement. It is caused by stricture of the duct or stone in the duct. Pain and swelling are associated with eating, then recede after several hours. Erythema may occur over the mass. A stone may be palpated in the duct, and occasionally pus can be stripped from the submandibular duct. Sialolithiasis may be found, however, in the presence of submandibular carcinoma.

A solitary squamous cell carcinoma metastatic to a submandibular lymph node in the absence of an obvious oral cavity primary lesion is uncommon (see Chap. 15). A primary submandibular neoplasm, benign or malignant, is a relatively rare event, but failure to recognize the possibility may result in an inappropriate, and sometimes disastrous, initial step in management.

Gallia and Johnson[16] reviewed 110 submandibular lesions in patients who underwent biopsy. Ninety-three (85%) were nonneoplastic, usually inflamed glands, and 9 (8%) were benign tumors. Eight patients (7%) had malignant lesions, of which three were lymphoma, three were metastatic carcinoma, and two were primary carcinoma of the submandibular gland.

Diagnostic Imaging

Introduction

MRI and CT are the examinations used for evaluating masses of the parotid region. Imaging is not usually indicated if the mass is discrete and freely mobile. Parotid inflammatory conditions sometimes will mimic mass lesions, and CT is preferred over MRI because of its ability to detect small calculi and ductal dilatation as signs of inflammatory disease. Ultrasound may be used for the evaluation of parotid inflammatory disease or masses. Some institutions use ultrasound to determine whether superficial lesions are intrinsic or extrinsic to the parotid gland. Ultrasound rarely is used for the evaluation of parotid disease at the University of Florida (Gainesville).

The main aims of imaging in parotid mass lesions are (1) to establish whether the mass is intrinsic or extrinsic to the parotid gland; (2) if the mass is intrinsic, to determine its relationship to the facial nerve; and (3) to evaluate the full extent of the lesion and determine whether it has morphologic features suggestive of an invasive process. Imaging can quickly narrow the diagnostic possibilities by excluding many of the extrinsic causes of masses of the parotid region. If the mass is intrinsic, superficial to the course of the facial nerve, and nonaggressive in its morphologic character, then surgeons are assured that superficial parotidectomy will suffice for initial diagnosis and management. If the mass is more extensive within the gland, patients can be informed about possible increased risk to the facial nerve inherent in the removal of the mass. If findings suggestive of malignancy are present, the study is extended to include the neck and the entire course of the facial nerve. Evaluation of the facial nerve usually is best done with gadolinium-enhanced MRI in multiple planes.

CT and MRI also are useful for evaluating masses in the region of the submandibular and sublingual glands.

Imaging of the Normal Anatomy

The anatomy of the major salivary glands was discussed earlier in this chapter. Their general appearance on MRI and CT is shown in Figures 27-4 and 27-5.[25]

The normal parotid and submandibular glands vary a great deal in size and appearance among individuals, depending mainly on the relative content of fat and glandular tissue. Masses generally are easier to see on CT when the glands contain more fatty tissue and rarely can be missed in a dense (nonfatty) gland. Since MRI has more tissue contrast options, a mass is virtually always visible on one of the pulse sequences.

The parotid is encapsulated; however, several natural routes of egress for tumor can be visualized on CT and MRI, including the following:

1. External carotid artery branches, especially the internal maxillary artery
2. Junction of the pterygoid venous plexus and deep veins with the retromandibular vein

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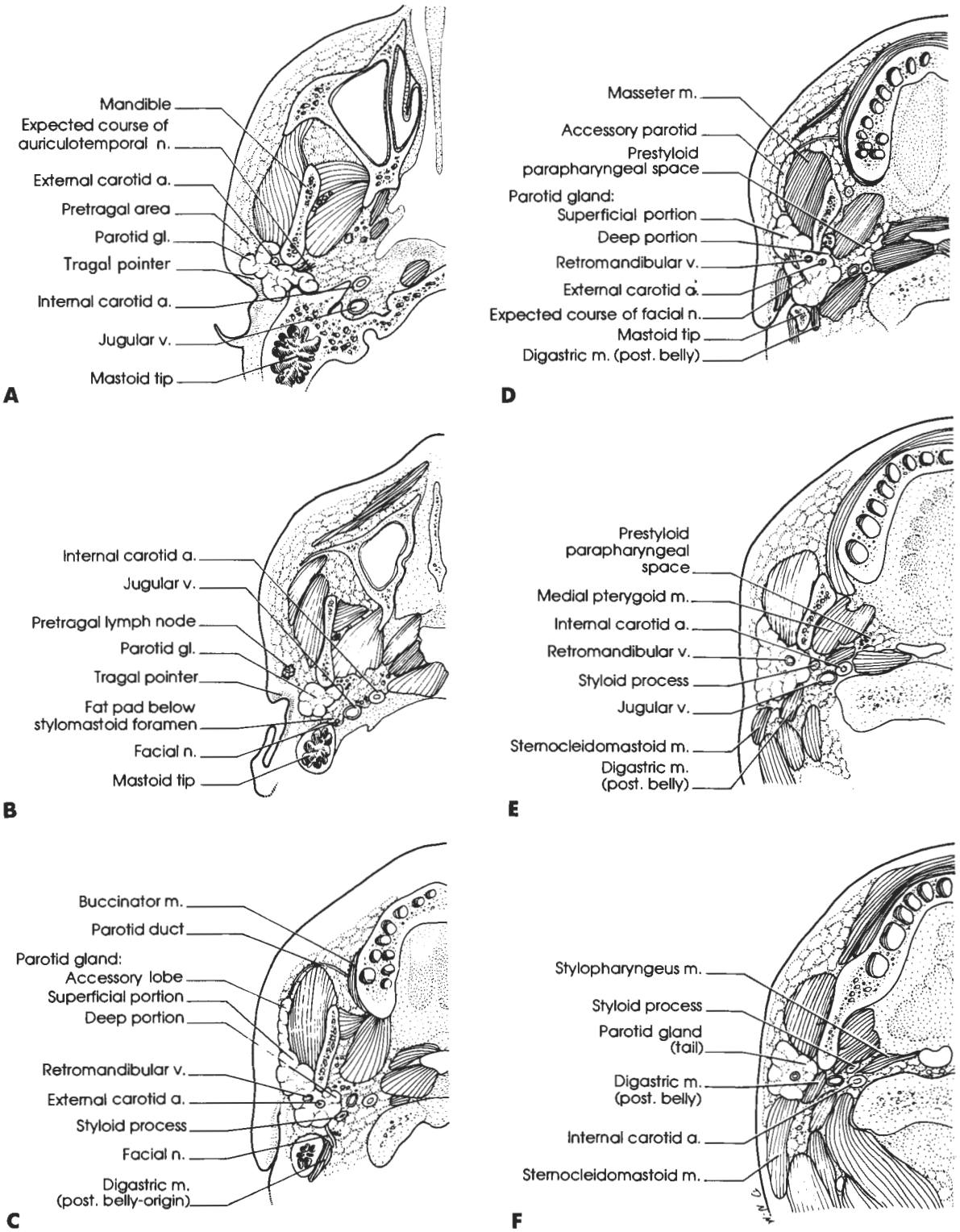

Figure 27-4. (*A* through *F*) Six line diagrams and correlated MR and CT sections showing normal anatomy seen in the transverse plane through the parotid gland. (Mancuso AA, Harnsberger HR, Dillon WP. Workbook for MRI and CT of the head and neck, ed 2. Baltimore, Williams & Wilkins, 1989:82–83)

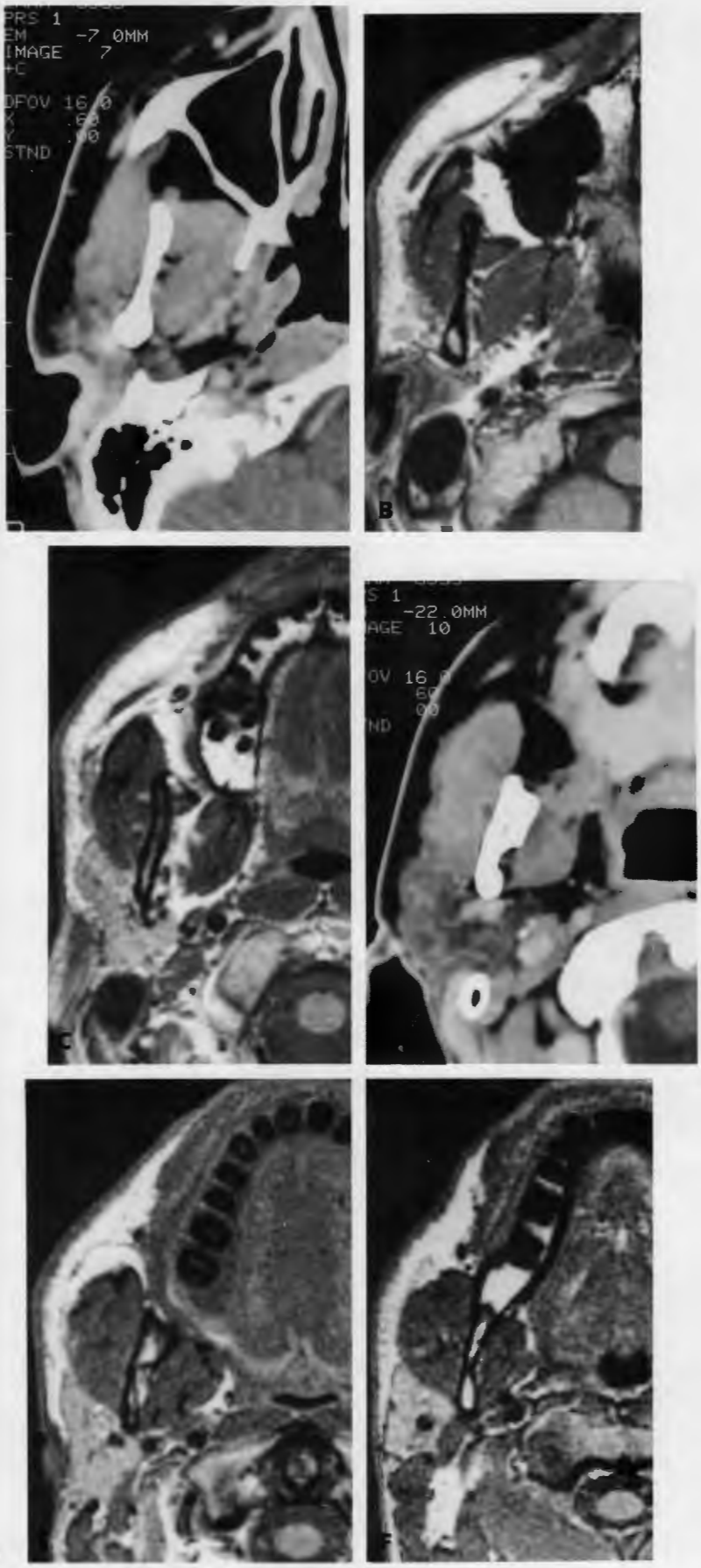

Figure 27-4. (*Continued*)

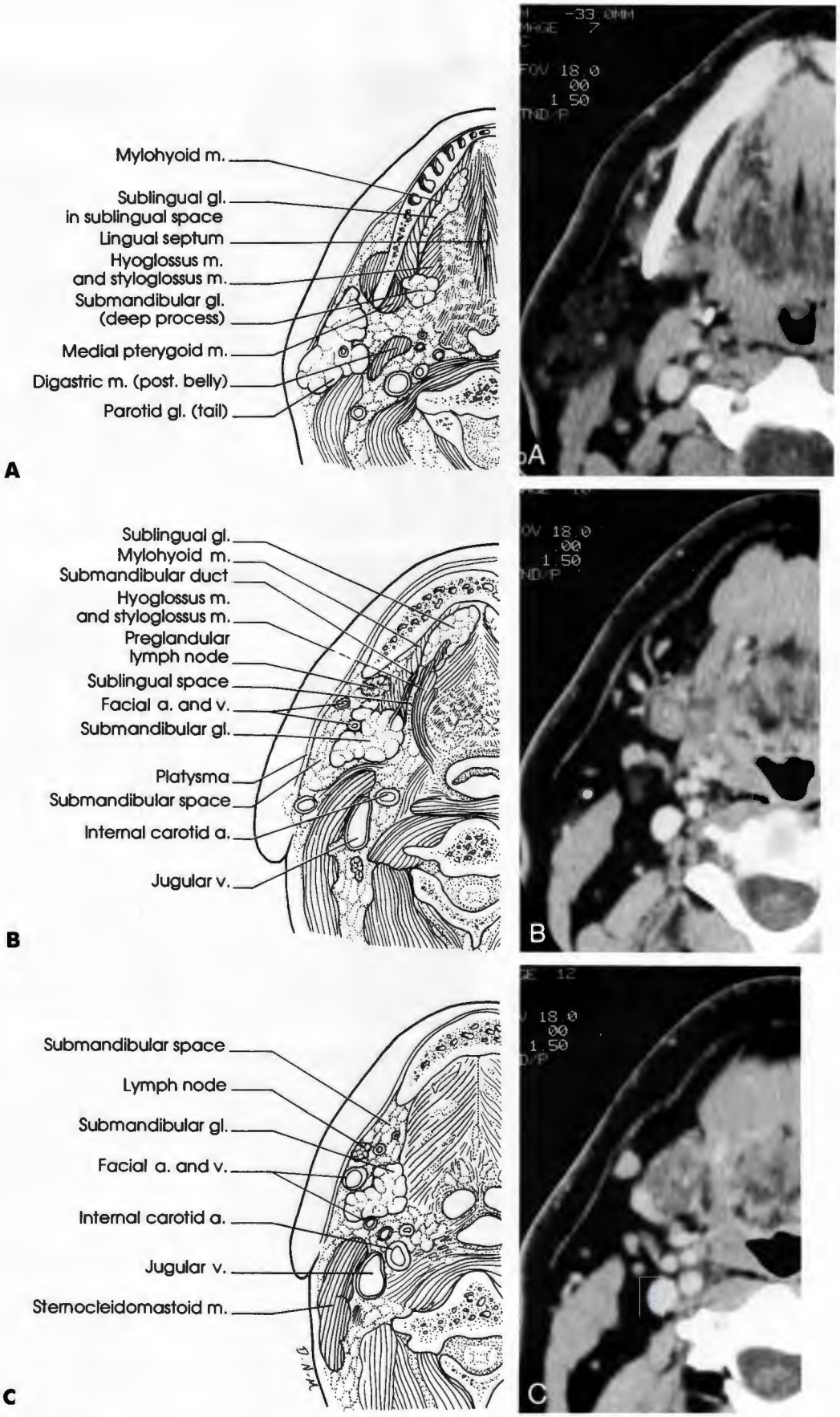

Figure 27-5. (*A* through *C*) Three line diagrams and corresponding CT and MR sections showing the normal anatomy through the submandibular gland and submandibular space as seen on transverse sections. (Mancuso AA, Harnsberger HR, Dillon WP. Workbook for MRI and CT of the head and neck, ed 2. Baltimore, Williams & Wilkins, 1989:84–85)

3. Course of the auriculotemporal nerve in the masticator space and the parotid gland
4. Facial nerve
5. Interface of the gland with the cartilages of the external ear

The facial nerve is the one most frequently in question. The surgical landmarks for identifying and dissecting the facial nerve are all visible on imaging studies. The following landmarks are used to identify the course of the facial nerve:

1. Descending facial canal
2. Stylomastoid foramen
3. Fat pad below the stylomastoid foramen
4. Tragal pointer
5. Digastric groove and posterior belly of the digastric muscle
6. External carotid artery and retromandibular vein

The ductal system of the parotid and submandibular gland is not normally visible except for the main parotid duct. When ductal structures are clearly visible within the glands, it almost always means they are dilated.

The sublingual glands are identified by their location in the partially fatty sublingual space on CT. On MRI, especially with injection of contrast material, the glandular tissue itself frequently is visible. The sublingual and submandibular glands come into contact at the posterior edge of the mylohyoid muscle.

Examination Technique

The basic high-resolution CT with contrast and MRI techniques described in Chapter 4 should be used. CT sections should be 3 mm thick and made parallel to the infraorbital meatal line for parotid studies; the gantry may be angled on the lower sections to avoid fillings. For submandibular or sublingual gland masses, sections should be parallel to the body of the mandible.

MRI is primarily done in the axial plane. Coronal and sagittal views are done in selected cases to evaluate the extent of a lesion relative to the temporal bone and skull base, or to evaluate the facial nerve. Noncontrast T1- and T2-weighted MRI usually suffices. Fat suppression techniques may be useful. Intravenous injection of paramagnetic contrast material is not necessary in many cases; however, it is extremely useful for evaluating perineural spread in selected cases. Paramagnetic contrast studies also may be useful if the lesion is aggressive or if the cervical nodes are to be evaluated (see Chaps. 4 and 6).

Indications for Imaging of the Parotid

DEFINITION OF MARGIN AND EXTENT OF A PAROTID REGION MASS. If the margins of a mass are not definite after physical examination, CT or MRI should be done. This will help determine whether the mass is intrinsic or extrinsic to the gland. This factor alone markedly alters the course of management in many patients (Figs. 27-6 and 27-7*A*) since so-called parotid masses frequently are of nonparotid origin.

DEFINITION OF THE RELATIONSHIP OF AN INTRINSIC PAROTID MASS TO THE FACIAL NERVE AND ITS MAJOR BRANCHES. In the past this was restricted to simply declaring whether the mass was superficial or deep to the main trunk of the facial nerve (see Fig. 27-7). It is now possible to refine this by describing the position of the mass in the gland relative to the usual surgical landmarks used to identify and dissect the facial nerve and its main branches (Fig. 27-8).

CHARACTERIZATION OF THE TYPE OF LESION PRESENT AND THE DEGREE OF INVASIVENESS BOTH WITHIN AND BEYOND THE PAROTID GLAND

Benign Mixed Tumors. The variable stromal and glandular tumor elements allow for great variability in the CT and MRI appearance of benign mixed tumors. They are typically well circumscribed and slightly lobulated on MRI and CT. A pseudocapsule may be visible, but frequently the wall is thin and seen only as an interface between the tumor and gland parenchyma (see Fig. 27-7*B*). Calcification and focally indistinct margins may be present.

Papillary Cystadenoma Lymphomatosum (Warthin's Tumor). These lesions always have well-circumscribed, smooth margins that may be lobulated. Often cystic components exist, and large areas of decreased signal may be present on T2-weighted MRI. Recognizing extraparotid, bilateral, or multiple tumors can help anticipate the correct diagnosis (Fig. 27-9).

Benign Lymphoepithelial Lesions (Godwin's Tumor). The more solid parts of these well-circumscribed tumors tend to be similar in density (CT) and signal intensity (MRI) to the normal gland, and the cystic regions are easier to identify. They are similar in appearance to Warthin's tumors. Multiple, bilateral lesions strongly suggest the presence of HIV infection.

Oncocytoma. These uncommon lesions are reported to be well circumscribed and homogeneously bright on T2-weighted MRI.

Low-Grade Malignancy. These usually are indistinguishable from benign mixed tumors or other benign tumors based on imaging findings. Focally, indistinct margins may provide a hint about their true nature. In general, on MRI, the interface between these tumors and the surrounding gland is well defined, and a capsule or pseudocapsule usually is not visible. Large cystic zones or generalized increased signal intensity on T2-weighted MRI may be present, but this is a nonspecific finding (Fig. 27-10). Calcification is unusual.

High-Grade Malignancy. An indistinct, infiltrating margin almost always will be present on CT and MRI. Spread beyond the confines of the parotid gland may be seen at presentation (see Figs. 27-8 and 27-11). These lesions tend to appear homogeneously solid, even on heavily weighted T2 images. Metastases to regional lymph nodes may be demonstrated (see Fig. 27-8).

Adenoid Cystic Tumors. On MRI and CT, these tumors range from smooth and well circumscribed to highly invasive, and usually are homogeneous in appearance (see Fig. 27-8). The more cribriform variety may be homogeneously bright on T2-weighted images because of the numerous cystic spaces filled with mucoid secretions.

Malignant Mixed Tumors. These tumors may appear identical to a benign mixed tumor or be focally or diffusely invasive.

Specific diagnosis of a parotid mass requires histologic examination, and the features just mentioned are

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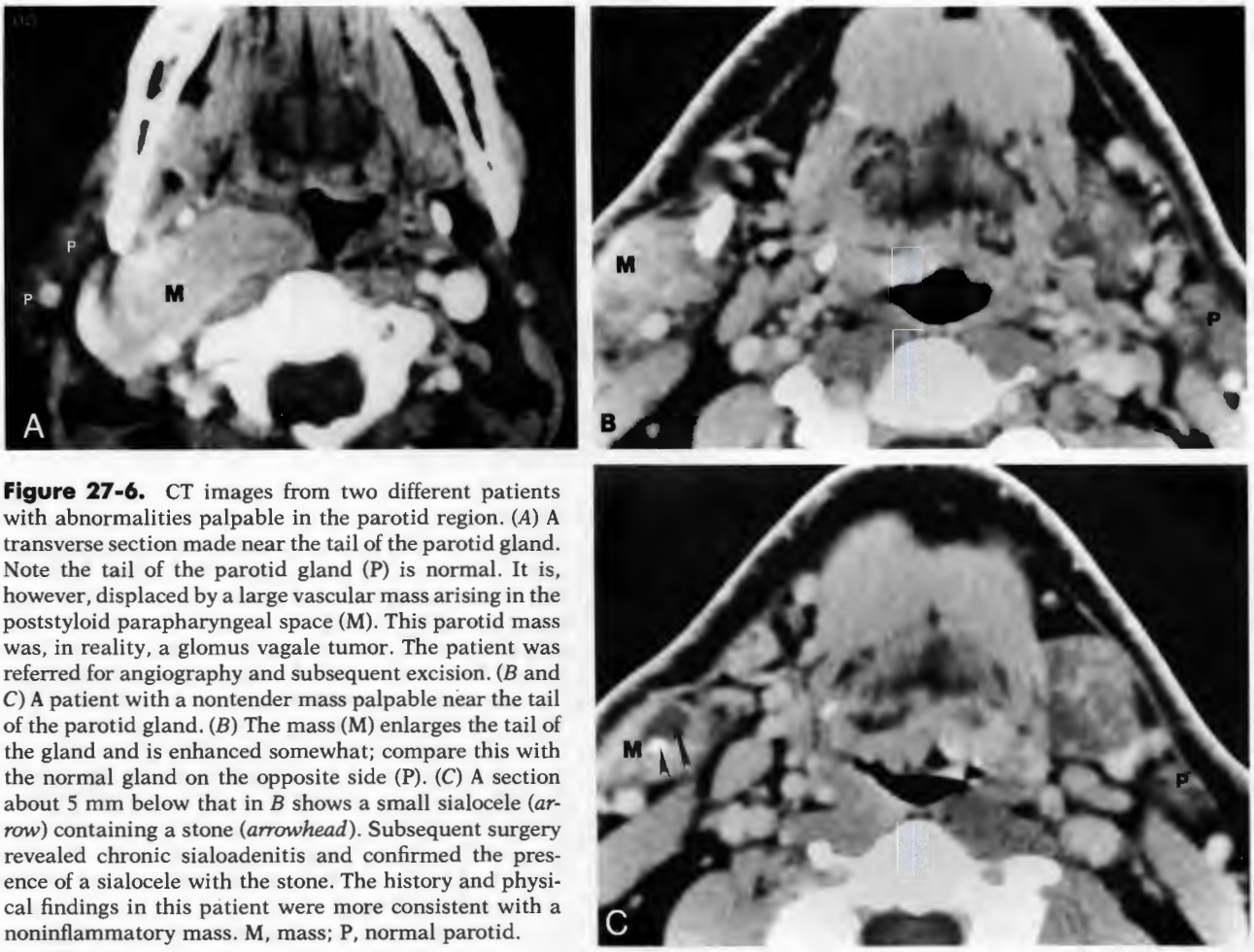

Figure 27-6. CT images from two different patients with abnormalities palpable in the parotid region. (*A*) A transverse section made near the tail of the parotid gland. Note the tail of the parotid gland (P) is normal. It is, however, displaced by a large vascular mass arising in the poststyloid parapharyngeal space (M). This parotid mass was, in reality, a glomus vagale tumor. The patient was referred for angiography and subsequent excision. (*B* and *C*) A patient with a nontender mass palpable near the tail of the parotid gland. (*B*) The mass (M) enlarges the tail of the gland and is enhanced somewhat; compare this with the normal gland on the opposite side (P). (*C*) A section about 5 mm below that in *B* shows a small sialocele (*arrow*) containing a stone (*arrowhead*). Subsequent surgery revealed chronic sialoadenitis and confirmed the presence of a sialocele with the stone. The history and physical findings in this patient were more consistent with a noninflammatory mass. M, mass; P, normal parotid.

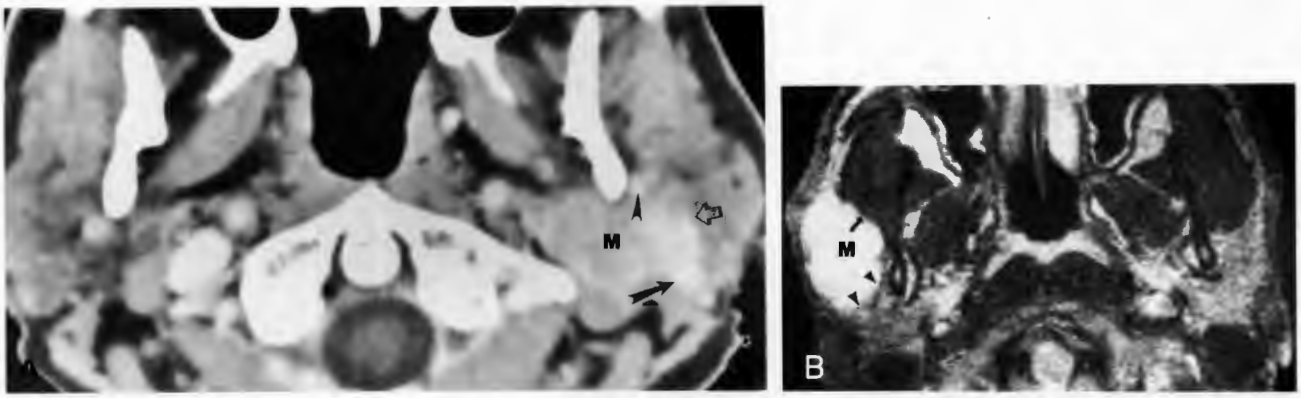

Figure 27-7. Imaging studies from two different patients presenting with parotid region masses. (*A*) Axial CT after injection of contrast medium. A mass intrinsic to the parotid gland (M) is present. It shows moderate enhancement. The mass displaces the retromandibular vein (*arrow*) laterally and posteriorly and pushes the external carotid artery and its branches (*arrowhead*) anteriorly and laterally. The mass fills the deep portion of the parotid gland, and a definite interface is seen between the tumor and the more superficial portion of the gland (*open arrow*). Needle biopsy at another institution revealed this to be an adenocarcinoma; its origin in the deep portion of the gland is obvious on the imaging study. (*B*) T2-weighted axial MRI of a patient with a mass in the parotid region. Mass (M) is very bright on the T2-weighted images; this is fairly typical of the well-differentiated salivary gland tumors. No definable capsule was seen, although a clear interface exists between the tumor and the masseter muscle (*arrow*) and between the tumor and the remainder of the normal parotid gland (*arrowheads*). This is a benign mixed tumor. The mass is clearly superficial to the facial nerve; however, one could see that it might prove difficult to resect this mass without some risk of injury to the peripheral branches of the facial nerve. In particular, both the zygomatic and buccal divisions would be at risk, judging from the position of the mass in the gland. The main trunk of the facial nerve is clearly deep to the medial margin of the lesion. Lesions such as these sometimes require removal of a cuff of muscle, as well as normal parotid tissue, to ensure complete excision.

Figure 27-8. Two different patients with malignant parotid carcinomas. (*A*) MRI through the midportion of the parotid gland shows an infiltrating tumor (T) with ill-defined margins. The mass appears to spread along the branches of the external carotid artery and retromandibular vein into the deep portion of the gland (*arrows*). The mass also appears to be involving and possibly spreading through the capsule of the gland (*arrowheads*). (*B*) A section taken approximately 1 cm below that in *A* shows multiple nodules within the gland (N), almost certainly representing metastatic intraparotid lymph nodes. Again, note the extension of the tumor to involve the capsule of the gland (*arrowhead*). (*C*) A coronal scan shows the major portion of the tumor (T) in the lower half of the parotid gland. This would be well below the main trunk of the facial nerve, which is expected to lie approximately where the arrow indicates. Note the extension of tumor superiorly and medially around the retromandibular vein (*arrowheads*), and between it and the external carotid artery (EC). Compare the infiltration of the tissue planes around these vessels with the normal retromandibular vein (RV) and external carotid artery (EC) on the opposite side. At surgery, a high-grade mucoepidermoid carcinoma with spread along these vascular structures, as well as perineural spread, was confirmed. (*D*) Axial CT of a patient with adenoid cystic carcinoma. This patient had a mass, about 15 by 15 mm, palpable in the superficial portion of the parotid gland. Also, paresis of cranial nerve VII was present. CT at approximately the level of the main trunk of the facial nerve shows a well-circumscribed portion of this adenoid cystic carcinoma (T); however, clearly the tumor has broken out of this circumscribed area and grown along the expected course of the facial nerve (*arrowheads*). These findings were confirmed at surgery.

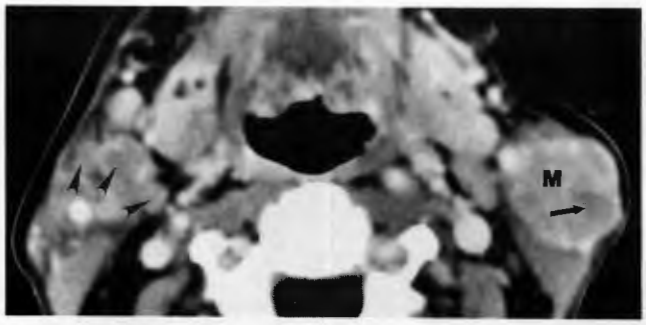

Figure 27-9. This patient had a left parotid region mass and some vague fullness in the right parotid region, but no discrete nodules were felt. The CT section made through the region of the tail of the parotid glands shows that a well-circumscribed mass (M) that was palpable on the left contained a cystic zone (*arrow*). The study also revealed multiple nodules in the region of the tail of the right parotid gland (*arrowheads*); these were both intrinsic and extrinsic to the gland as seen on other views. This made the diagnosis of Warthin's tumor very likely. Other differential possibilities included multiple lymphoepithelial tumors, multiple lymph nodes, or possibly, multiple cystic lesions, as might be seen in end-stage autoimmune sialoadenitis. This patient did have Warthin's tumors.

only suggested as a preoperative aid to differential diagnosis. More important, CT or MRI is used to define the extent of aggressive masses as they spread to surrounding areas.

DETERMINATION OF THE EXTENT OF PERINEURAL TUMOR SPREAD IN PATIENTS WITH KNOWN OR SUSPECTED MALIGNANCIES. Gross perineural spread of tumor along the facial nerve occasionally is visible within the gland on CT or MRI (see Figs. 27-8, 27-11, and 27-12). It may also be manifested by thickening of the nerve as it is seen in the fat pad below the stylomastoid foramen, or along its course through the temporal bone and back to the brain stem (see Chap. 25, Fig. 25-3). Negative results from imaging studies do not exclude perineural spread.

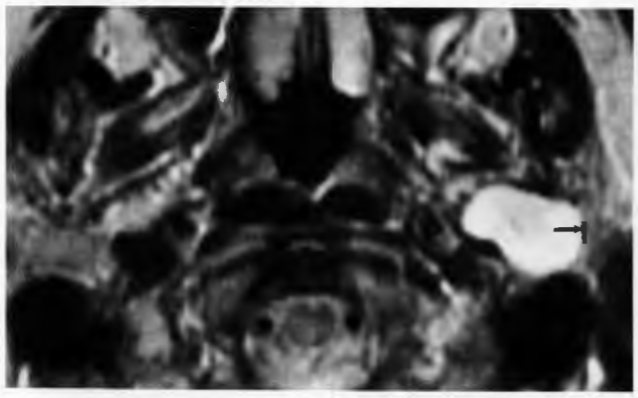

Figure 27-10. This patient had a palpable abnormality in the parotid region. This heavily T2-weighted axial MRI showed a well-defined mass centered in and filling the deep portion of the gland, with some extension into the superficial portion (*arrow*). The lesion is homogeneously bright on this T2-weighted image, as well as being well circumscribed. This was an acinic cell carcinoma. Low-grade mucoepidermoid carcinomas and adenoid cystic carcinomas also may have a similar appearance, even though they are malignant tumors.

Indications for Imaging of the Submandibular Gland

MRI or CT is almost always capable of differentiating a submandibular gland mass from an extrinsic mass (see Chap. 6, Fig. 6-29). Occasionally, other masses, such as a ranula, dermoid, thyroglossal duct cyst, or lesion of neural origin, will mimic a submandibular gland or nodal lesion. Inflammatory disease usually will be manifested by ductal dilatation and the presence of stones (see Fig. 27-6).

If the mass is intrinsic to the gland, it may be malignant, and the study should be extended to include cervical lymph nodes (Fig. 27-13).

Biopsy Technique

Parotid Gland

Imaging by CT or MRI before the operation strongly suggests whether the lesion is highly invasive or well circumscribed and whether the facial nerve is likely to be involved. Excisional and incisional biopsies are not recommended, because they increase the risk of recurrence and facial nerve damage and increase the surgical morbidity by adding a wide removal of the biopsy site. Routine use of fine-needle aspiration requires a pathologist skilled in the interpretation of the aspirate. Needle biopsy usually is reserved for inoperable or recurrent lesions in our own practice.

Submandibular Gland

Needle biopsy may be indicated, and is useful if a malignant tumor is diagnosed. Needle biopsy, if negative, often is misleading and may delay diagnosis. If a careful search of the head and neck area fails to reveal a primary mucosal lesion, the submandibular triangle may be dissected as the biopsy procedure. Incisional or excisional biopsy increases the risk of tumor recurrence, even when followed by appropriate treatment, and increases the surgical morbidity by requiring wide excision of the biopsy site.

Staging

The American Joint Committee on Cancer (AJCC) staging for tumors of the salivary gland is listed below.[4]

TX:	Minimum requirements to assess the primary tumor cannot be met
T0:	No evidence of primary tumor
T1:	Tumor 2 cm or less in greatest diameter without significant local extension*
T2:	Tumor more than 2 cm but not more than 4 cm in greatest diameter without significant local extension*
T3:	Tumor more than 4 cm but not more than 6 cm in greatest diameter without significant local extension*
T4A:	Tumor over 6 cm in greatest diameter without significant local extension*

* Significant local extension is defined as evidence of tumor involvement of skin, soft tissues, bone, or the lingual or facial nerves.

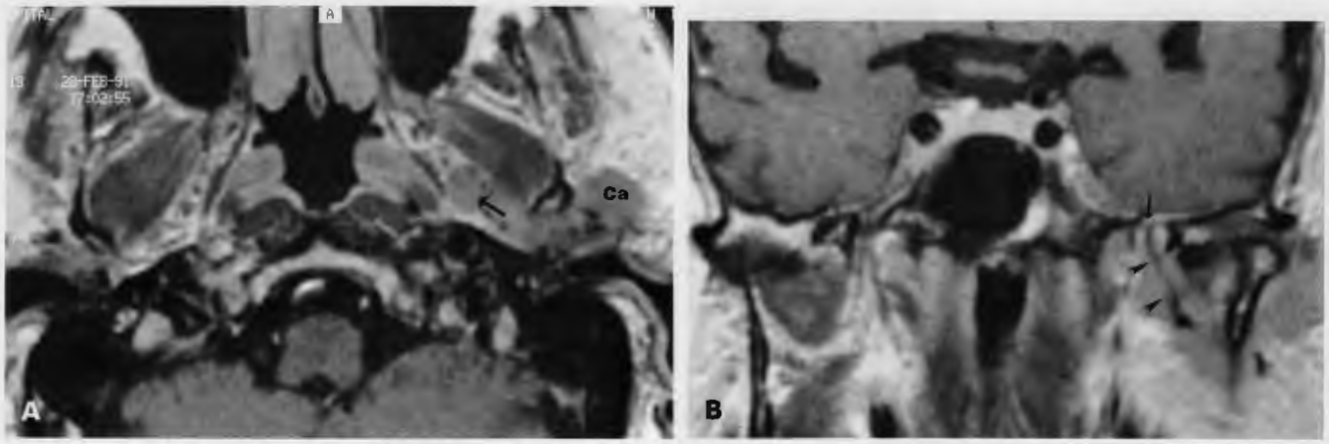

Figure 27-11. This patient had a parotid region mass and some pain in the periauricular region. (*A*) Axial, T1-weighted, contrast-enhanced MRI through the upper parotid region shows the poorly differentiated adenocarcinoma (Ca) in the upper portion of the gland. It extends along the course of the auriculotemporal nerve to involve the mandibular nerve within the masticator space (*arrow*). (*B*) A coronal section confirms the extent of the disease as seen on the axial section and shows the tumor extending along the course of the mandibular nerve (*arrowheads*) to the foramen ovale (*arrow*).

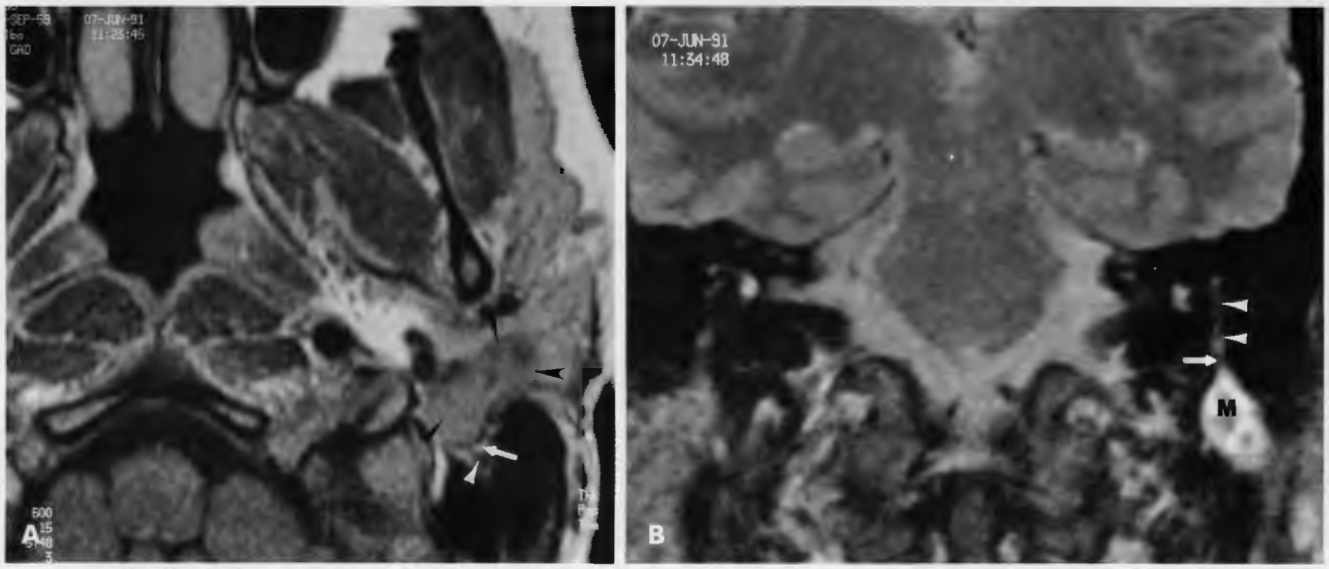

Figure 27-12. MRI of a 32-year-old woman who had a parotid mass. The facial nerve function was normal. (*A*) An axial T1-weighted image, made through the expected level of the main trunk of the facial nerve, shows a well-circumscribed mass (*arrowheads*) growing along the expected course of the facial nerve and into the fat pad just below the stylomastoid foramen (*arrow*). The facial nerve itself (*white arrowhead*) may actually be visible, somewhat posteriorly displaced within this fat pad. (*B*) A T2-weighted coronal image through the descending facial canal (*white arrowheads*) shows the inhomogeneous, but basically bright, mass (M) extending to, but not definitely into, the stylomastoid foramen (*arrow*). The differential diagnosis was considered to be a schwannoma or neurofibroma of the seventh nerve versus an adenoid cystic carcinoma. The patient was informed of these possibilities. Parotid exploration revealed a schwannoma of cranial nerve VII. The patient elected to be observed rather than risk the loss of seventh nerve function if the lesion turned out to be benign at surgery. It is currently 1 year after exploration, and follow-up MRI has shown no interval growth in the lesion.

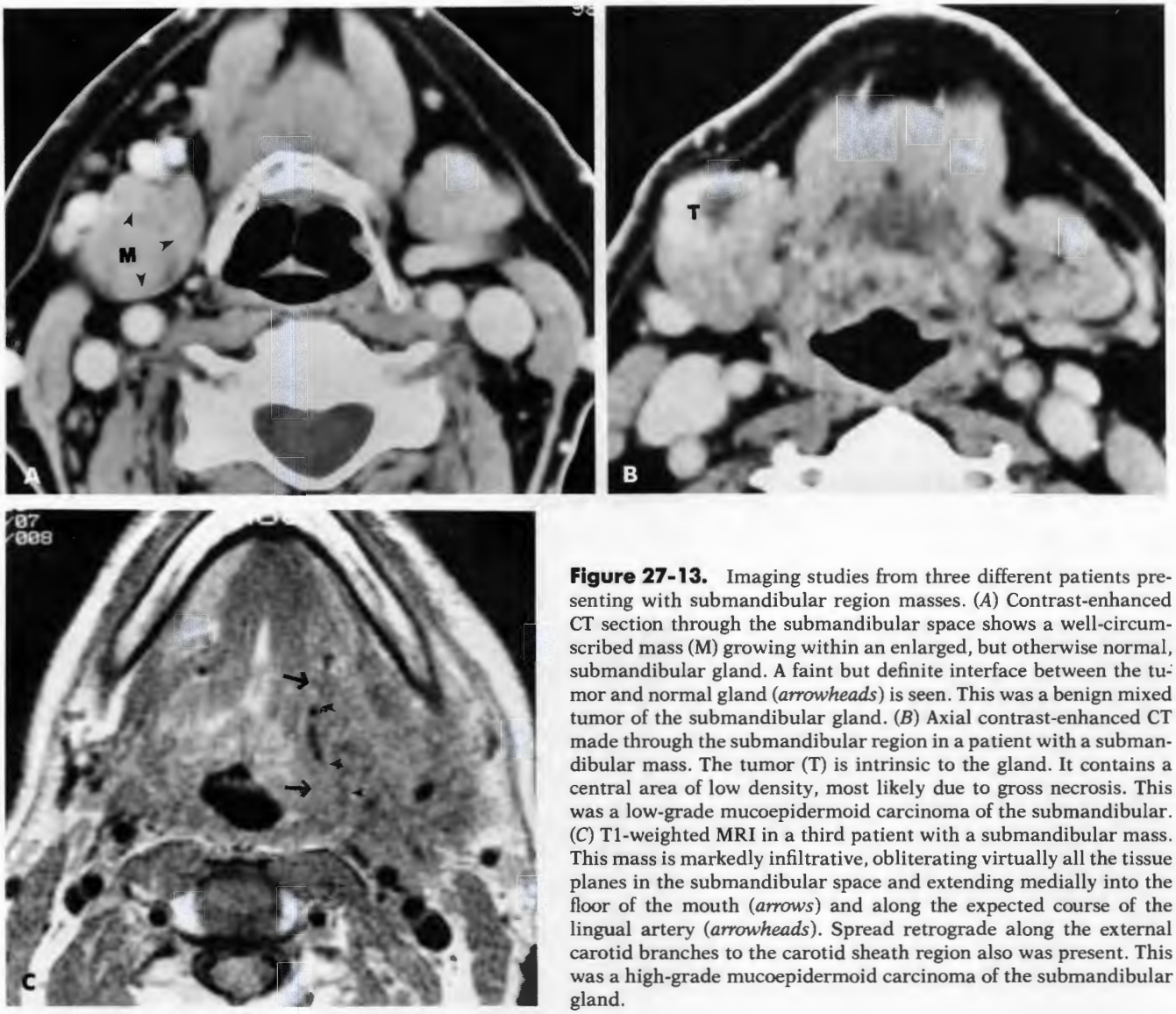

Figure 27-13. Imaging studies from three different patients presenting with submandibular region masses. (*A*) Contrast-enhanced CT section through the submandibular space shows a well-circumscribed mass (M) growing within an enlarged, but otherwise normal, submandibular gland. A faint but definite interface between the tumor and normal gland (*arrowheads*) is seen. This was a benign mixed tumor of the submandibular gland. (*B*) Axial contrast-enhanced CT made through the submandibular region in a patient with a submandibular mass. The tumor (T) is intrinsic to the gland. It contains a central area of low density, most likely due to gross necrosis. This was a low-grade mucoepidermoid carcinoma of the submandibular. (*C*) T1-weighted MRI in a third patient with a submandibular mass. This mass is markedly infiltrative, obliterating virtually all the tissue planes in the submandibular space and extending medially into the floor of the mouth (*arrows*) and along the expected course of the lingual artery (*arrowheads*). Spread retrograde along the external carotid branches to the carotid sheath region also was present. This was a high-grade mucoepidermoid carcinoma of the submandibular gland.

T4B: Tumor of any size with significant local extension*

The AJCC staging for neck nodes also is listed:

NX: Minimum requirements to assess the regional nodes cannot be met

N0: No evidence of regional lymph node involvement

N1: Evidence of regional lymph node involvement

TREATMENT

Selection of Treatment Modality

Surgical resection is the mainstay of treatment for tumors of the major salivary gland. The concept of adding radiation therapy to the surgical management of tumors of the salivary gland has been rediscovered. Ahlbom[3] concluded in 1935, on the basis of 254 cases managed at the Radiumhemmet, Stockholm, that a combination of surgery and irradiation produced a relatively greater frequency of local control than is customarily seen with surgery or radiation alone. He also observed that the regional lymph nodes should be irradiated along with the primary site.

In 1940, Cade[9] made the same observation from his records, namely that either preoperative or postoperative irradiation, or both, greatly added to the efficacy of the surgical treatment of this group of tumors.

Rafla-Demetrious[32] reviewed the experience of the Royal Marsden Hospital (London) with tumors of the major and minor salivary gland in 1970. His monograph gives several examples of patients managed entirely by radiation therapy, thus demonstrating the radiocurability of both benign and malignant neoplasms.

Jesse and Fletcher of M.D. Anderson Hospital (Houston) pioneered the concept of combining surgery and radiation therapy to conserve the facial nerve.[18]

* Significant local extension is defined as evidence of tumor involvement of skin, soft tissues, bone, or the lingual or facial nerves.

Parotid Gland

BENIGN MIXED TUMORS. Surgical removal with a cuff of normal tissue is the treatment of choice. This margin can be accomplished by a superficial lobectomy in most cases. Postoperative radiation therapy is considered when tumor spill is recognized[18] or malignancy is suspected. The few recurrences after operation alone usually are successfully managed by further resection, but the risk of facial nerve damage is increased. The routine use of postoperative radiation therapy is not advised, especially in younger patients, because of a slight risk of radiation-induced malignancy and other late complications; these factors must be balanced against the substantial risk of facial nerve loss that is associated with operation for recurrent disease.

LOW- TO MODERATE-GRADE MALIGNANCIES. The majority of low- to moderate-grade malignancies can be managed by a superficial lobectomy; a few require total parotidectomy. Postoperative irradiation usually is not needed, but it may be used in the case of positive or close margins, rupture of the capsule, surgical dissection close on the facial nerve, or recurrent tumor.

ADENOID CYSTIC CARCINOMA. Microscopically, adenoid cystic carcinoma appears as a low-grade malignancy and often has a history of slow growth, but it is best approached as a *high-grade malignancy*. The management of this histologic type can be one of the most frustrating experiences in oncologic practice; it frequently demonstrates a capricious behavior reminiscent of malignant melanoma. A seemingly slow-growing, localized lesion that is completely excised and given generous postoperative radiation therapy may develop late evidence of local–regional recurrence or distant metastasis. These tumors are radiosensitive, but the term *curative* must be applied with caution. The natural history of this tumor requires a treatment strategy that gains the maximum local–regional control and survival rates with acceptable morbidity. The usual approach is wide surgical resection followed by radiation therapy to a generous volume including the perineural pathways and ipsilateral neck. Wide surgical excision may be easier to recommend than to perform, and positive margins are frequent. Borderline resectable lesions should be considered for preoperative radiotherapy, or even radiotherapy alone.

Management of the regional lymph nodes is described in the next section.

Asymptomatic, slowly evolving lung metastasis may be present at the time of initial diagnosis, or at a time when patients present for management of a local or regional recurrence. A few of these patients live several years with distant metastases, and the approach to management of the local–regional problem may not differ much from that used in patients without distant metastasis.

HIGH-GRADE TUMORS. High-grade neoplasms usually are managed by parotidectomy and postoperative radiation therapy. The risk for local recurrence is 35% to 55% with surgery alone, and the addition of postoperative irradiation can reduce the risk to about 10% to 15%. If the facial nerve is uninvolved by tumor, the mass usually can be removed, leaving the nerve intact. If the tumor extends through the isthmus to the deep portion of the gland, the nerve is gently retracted and the deep portion of the gland is excised in continuity with the superficial lobe. If the tumor merely lies adjacent to the nerve, it may be carefully dissected from the nerve. If the tumor grossly invades the facial nerve, one or more branches will have to be sacrificed. Surgeons should not attempt to save a functioning facial nerve that is invaded by tumor in the hope that postoperative irradiation will take care of the residual disease; tumor invading nerves represents a situation unfavorable for cure, even with high doses. Radiation therapy will not apologize for an incomplete gross resection.

The lymph nodes adjacent to the parotid gland are removed in continuity with the specimen. A neck dissection is added only if the lymph nodes of the neck are clinically involved. Postoperative irradiation is added in nearly all cases, regardless of the margins, and includes the entire ipsilateral neck.

Preoperative radiation therapy should be considered for patients with unresectable disease; the masses become smaller and more discrete and develop a tougher capsule, which aids dissection. Unresectable tumors are treated by radiation therapy alone, usually a combination of external-beam and interstitial implant therapy; a few cures are reported for these cases.

See Chapter 25 for management of squamous cell carcinoma that is metastatic to lymph nodes of the parotid area.

Submandibular Gland

Submandibular triangle dissection is used to make the diagnosis. If frozen-section diagnosis shows a malignant lesion and the nerves, mandible, or soft tissues are not involved, the operation may be concluded and postoperative irradiation is given to the submandibular bed and ipsilateral neck. If a simple excision of the malignant mass has been performed and the margins are negative or only microscopically positive, radiation therapy only is recommended. If perineural invasion, bone invasion, a clinically positive lymph node(s), or extension to contiguous soft tissues occurs, then the resection is enlarged to encompass the necessary areas. This resection may include the mandible, mylohyoid muscle, digastric muscle, adjacent floor of the mouth or tongue, and involved nerves and also a neck dissection. For lesions fixed to the mandible but not invading bone, the inferior border of the mandible may be resected. Postoperative radiation therapy is added.

Unresectable lesions, after a biopsy, are treated with preoperative radiation therapy or radiation therapy alone.

Surgical Treatment

Lateral Lobe Parotidectomy (Superficial Parotidectomy)

The initial approach for resectable lesions confined to the lateral lobe is exploration and en bloc lateral lobectomy, both for diagnosis and for treatment. Lumpectomy, enucleation, or excisional biopsy should not be done because the recurrence rate, even for benign lesions, is high, the surgical field is violated, and damage to the facial nerve is likely.

An incision is made in the preauricular crease and is then curved under the ear lobe posteriorly and into the upper neck. An anterior cheek flap is developed to expose

the fascia and underlying gland. The upper neck and inferior portion of the ear then are exposed. Singleton and Cassisi[33] reported that thin flaps are more likely to produce gustatory sweating than thick flaps. The facial nerve must be identified in all superficial parotidectomies; the nerve is in a more superficial position at the stylomastoid foramen in children. Once this is accomplished, sharp dissection is carried out between the mass and the facial nerve (Fig. 27-14). No cleavage plane occurs between the nerve and the gland, or between the lateral lobe and the deep lobe.

The lateral lobectomy may be modified for different anatomic situations. Neoplasms involving the isthmus may attach to the fascia of the masseter, and a cuff of muscle must be included to satisfy the deep margin.

The large, bulky tumors require a modification in approach in order to identify the facial nerve. One method is an inferior dissection to first identify a lower branch, and then trace this branch to the main trunk.

Total Parotidectomy

The term *total parotidectomy* is a slight exaggeration since it is nearly impossible to remove all of the glandular tissues. It is difficult at the operating table to distinguish between the borders of the gland and the adjacent fat; and if the facial nerve is preserved, the term *total* is even less appropriate.

Total parotidectomy includes the entire gland and a cuff of normal tissue, and it may be done with complete sparing of the facial nerve or with partial or complete resection of the facial nerve. The facial nerve usually can be spared for a benign tumor that extends toward the deep lobe and for some large low-grade or even small, discrete malignant tumors that invade the isthmus or deep lobe. Some normal parotid tissue remains, and the chance of residual tumor is more likely.

A radical parotidectomy may include the facial nerve, the skin, the superficial fascia and platysma muscle, a portion of the masseter, the posterior digastric muscle, a section of the internal pterygoid muscle, the stylohyoid muscle, the tip of the mastoid, a portion of the sternocleidomastoid muscle, and sometimes the external auditory canal. A rim or partial mandibulectomy is required when the tumor is fixed to the periosteum or actually invades the mandible. When pain or paresthesia is present, the auriculotemporal nerve should be explored to the base of the skull.

Either elective neck dissection or elective neck irradiation is advised for high-grade lesions, since the risk of lymph node metastasis is about 30%. If the lymph nodes are clinically positive, a neck dissection is done.

Benign tumors arising from the deep lobe and prestyloid parapharyngeal space are approached by first doing a lateral lobectomy to gain exposure and preserve the facial nerve. The tumor mass then is removed by retracting the branches of the facial nerve. It may be necessary to divide the mandible behind the third molar to expose a large deep-lobe mass.

Nerve Grafts

See the section on complications of surgical treatment for a discussion of nerve grafts.

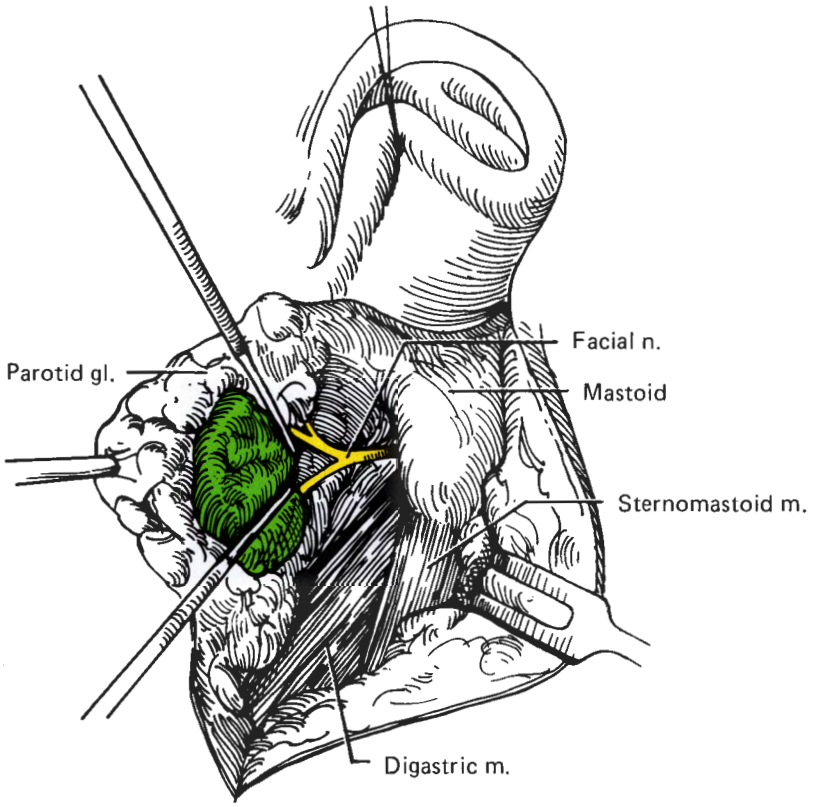

Figure 27-14. Lateral lobectomy for a mass confined to the left lateral lobe. Sharp dissection proceeds along the course of the facial nerve.

Irradiation Technique

Tumors of the salivary glands have an undeserved reputation for being resistant to radiation therapy. There are instances of unresectable or recurrent tumors controlled by radiation therapy alone, and even examples of benign mixed tumors that disappear or remain under control with radiation therapy alone. Little difference is seen in the response of the various malignant histologic types, except that the malignant mixed tumor may respond less often than the others.

Parotid Gland

Radiation therapy plays its major role as an adjunct to surgery and usually is given postoperatively, although preoperative treatment may be considered in special situations. Postoperative irradiation is indicated for most high-grade lesions, for close or positive margins, for tumors involving the deep lobe, for recurrent tumors, and for multiple regional lymph node metastases.

The minimum treatment volume includes the parotid bed and upper neck nodes. Perineural involvement indicates enlargement of the portals to cover the nerve pathways. The entire neck is electively irradiated for high-grade lesions or for clinically positive nodes in the radical neck dissection specimen. The tumor dose to the primary area is 6000 cGy over 6 weeks if no gross residual is present; higher doses are used for gross disease or positive margins. No good data show a difference in dose required for the various histologic types, although the treatment failure rate for malignant mixed tumors may be greater.[20,21]

INTERSTITIAL IMPLANT. Interstitial implant may be used for postoperative irradiation if the primary tumor was located in the preauricular portion of the superficial lobe. A modified two-plane implant, with the deep plane extended into the retromandibular area, for 6000 cGy over 6 to 7 days, will cover the tumor bed, but it gives inadequate coverage of the retromandibular portion of the parotid bed. Alternatively, the interstitial implant may be added as a boost treatment after external-beam therapy to increase the dose to a specific area that is at especially high risk owing to a positive margin, to give additional irradiation along a scar, or to administer a higher dose to a residual mass when irradiating unresectable or locally recurrent disease. The implant is relatively simple to perform. To gain the margin along the external ear canal, the needles and sources usually penetrate the tragal cartilage. The implantation of the retromandibular deep lobe area is a blind procedure, but it may be done safely (see Chap. 25, Fig. 25-22).

EXTERNAL BEAM. The majority of patients with tumors of the parotid gland are managed by external-beam radiation therapy. Two basic techniques are used. One technique involves a wedge pair, with the direction of the portals being superior and inferior to direct the exit dose away from the orbits and oral cavity. Anterior- and posterior-directed wedge portals often are possible, as long as the technique avoids exit irradiation to the contralateral orbit. The disadvantage of the angled wedge technique is the inability to shape the fields to avoid irradiation of some normal tissues in the high mastoid–retroauricular area.

A second basic technique uses simple ipsilateral portals that are shaped to fit the anatomy[27] (Fig. 27-15). A treatment scheme using a combination of high-energy photons and high-energy electrons produces a homogeneous dose distribution and delivers 3000 cGy or less to the opposite salivary glands (see Chap. 14). This technique is preferred over the wedge-pair portals because of the ability to shape the fields, to reduce them easily when desired, and to easily attach an ipsilateral anterior low-neck field. In patients having malignancies with a proclivity to perineural spread, one must include the in-

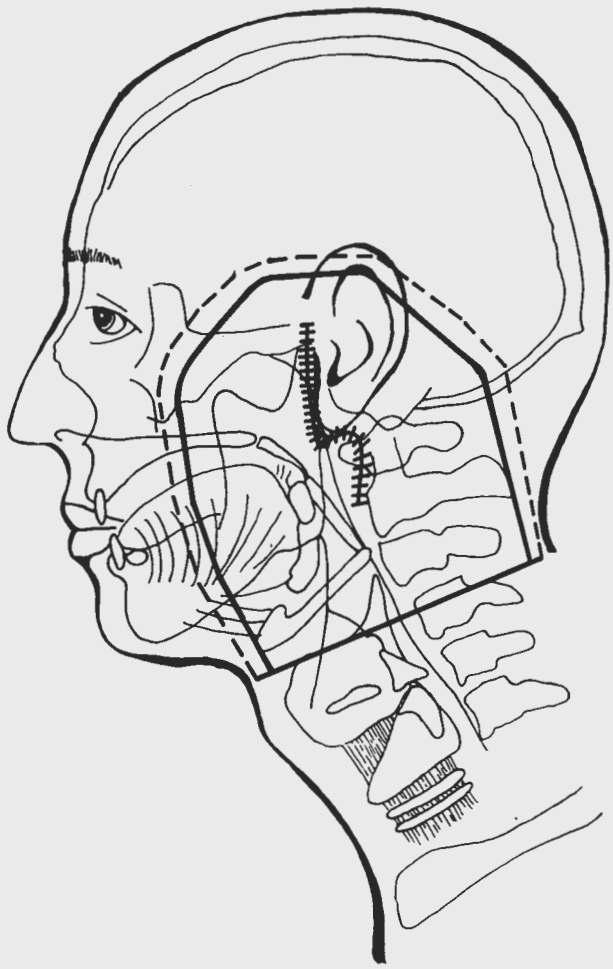

Figure 27-15. Example of a portal for postoperative irradiation of cancer of the parotid gland with a combination of photons and electrons. The anterior border is usually at the anterior border of the masseter muscle; the inferior border is at the top of the thyroid cartilage. Superiorly and posteriorly, the entire parotid and surgical bed are included. Electron portal (*dashed lines*) is 1 cm larger than photon portals, because of the constriction of electron isodose lines at depth. An intraoral stent made of lead or Lipowitz's metal will further reduce contralateral irradiation. About 2 to 3 cm of the distal facial canal is included in this example. The doses to the temporal lobe and posterior fossa must be calculated. (Parsons JT, Mendenhall WM, Bova FJ, Million RR. Head and neck cancer. In: Levitt ST, Khan FM, Potish RA, eds. Levitt and Tapley's technological basis of radiation therapy: practical clinical applications, ed 2. Philadelphia, Lea & Febiger, 1992:227)

traosseous pathway of the facial nerve and the auriculotemporal nerve. Tumor may spread peripherally, as well as proximally, along the facial nerve so that adequate coverage along the peripheral distribution also is required. When tumor involves the deep lobe or otherwise extends near the midline, it is necessary to use parallel opposed photon portals weighted to the side of the lesion for the first portion of the therapy. Calculation of dose to the brain stem and spinal cord must be precise in these plans.

The dose to the parotid bed depends on the level of risk for residual disease: 5000 cGy over 5 weeks to 6000 cGy over 6 weeks is prescribed, depending on the risk factors for recurrence; higher doses are recommended for positive margins or gross residual disease.

An interstitial implant boost is recommended to boost treatment of gross disease whenever technically possible; the dose in these cases often will be 5000 to 6000 cGy from external-beam therapy plus 2000 to 3500 cGy from the implant. (See Chap. 25, section on parotid area lymph node metastasis.)

Submandibular Gland

Ipsilateral external-beam portals are tailored to the extent of disease found in the surgical dissection. The possible sites of local recurrence include the submandibular triangle, adjacent oral cavity, pterygomaxillary fossa, base of the skull, parotid gland, and neck. When major nerve trunks are involved, the nerves usually are included beyond the margin of dissection, even if the final nerve margin is clear. Skip metastasis along nerves is probably uncommon, but is reported. If final nerve margins are positive, the nerves are included to their origin (eg,gasserian ganglion). The entire ipsilateral neck always is included; the opposite neck usually is not at risk. The beam energy depends on the depth at risk. An electron beam, photon beam, or a combination of both is selected, depending on the situation. The postoperative dose is 6000 to 6500 cGy over 6 to 6½ weeks if there is no gross residual disease. Higher doses are used if gross residual disease is present. An interstitial implant may be added to the tumor bed if residual disease is suspected.

Management of Recurrence

Benign Mixed Tumors

Recurrent benign mixed tumors often can be treated with another operation, but the risk of damage or sacrifice of the facial nerve is higher because of the presence of scar tissue from previous operations. Postoperative radiation therapy usually is added on an individualized basis, especially when recurrence is multinodular, the pathologist is unsure about the benign nature, or a history of rapid growth exists. If a subsequent operation for recurrence is likely to cause a serious seventh nerve deficit, then radiation therapy usually is recommended. In patients with unresectable benign mixed tumors, salvage may be achieved by radiation therapy alone. Observation alone is appropriate for some recurrences.

Malignant Tumors

Malignant tumors that recur after an operation are managed by another operation and postoperative radiation therapy or, if unresectable, by radiation therapy alone.

RESULTS OF TREATMENT

Benign Mixed Tumors

Enucleation or excision with a narrow rim of normal tissue eventually will result in a local recurrence rate of about 20% after 10 to 15 years of follow-up. Rafla-Demetrious[30] reported only a 2.7% recurrence rate when enucleation or excision was followed by postoperative radiation therapy. Gleave and coworkers[17] reported a 1.9% recurrence rate after capsular dissection in 257 patients, and a 1.8% recurrence rate after nerve dissection in 112 patients. Forty-nine patients received postoperative radiation therapy owing to tumor spill or question of malignancy; one patient in this group had tumor recurrence.

Piorkowski and Guillamondegui[29] reported on the management of 45 patients who had recurrent benign mixed tumors and 13 patients who had had incomplete excision. The operative procedure was individualized and varied from excision of a tumor nodule to total parotidectomy with total resection of the facial nerve. Only three patients received postoperative radiation therapy. The recurrence rate was 14%. The facial nerve was resected partially in 24% of cases and completely in 16%.

Fee and associates[15] reported 65% surgical success for the first recurrence, whereas 29% were controlled after the second and 25% after the third recurrence. Permanent facial nerve paralysis occurred in 29% of cases, usually involving 20% or less of the nerve. Gleave and coworkers[17] reported a 12.6% recurrence rate after operation for recurrent benign mixed tumors of the parotid gland; 41% had postoperative radiation therapy. The incidence rate of permanent facial nerve injury was 12.6%.

Death due to benign mixed tumor should be a rare event.

Malignant Tumors

Parotid Gland

Woods and coworkers[38] from the Mayo Clinic (Rochester, MN) reported the results for the treatment of 228 malignant parotid tumors for two time periods. There was a minimum 5-year period of observation for all cases. In the period 1940 to 1954, local excision or biopsy followed by irradiation was used in 65% of cases, and all or a portion of the facial nerve was sacrificed in only 20% of cases. The local recurrence rate was 17% (3 of 18) for low-grade carcinomas (low-grade mucoepidermoid and acinic cell) and 58% (38 of 65) for high-grade carcinomas. In the second period (1955 to 1969), local excision or biopsy plus irradiation was used in only 8% of cases, and a total of 17% received postoperative irradiation. The initial operations were more radical, with 34% of patients having all or a portion of the facial nerve removed. The local recurrence rate was 6% (5 of 78) for low-grade carcinomas and 53% (35 of 66) for high-grade carcinomas.

Spiro and colleagues[34] reported the results from the Memorial Sloan-Kettering Hospital (New York) for 288

TABLE 27-3. Cancer of the Parotid Gland: Treatment Failure According to Stage*

Site	Treatment Failure (%)†		
	Stage I (104 Patients)	Stage II (83 Patients)	Stage III (99 Patients)
Local recurrence	7	21	58
Uncontrolled neck disease‡	1	10	33
Distant metastasis§	2	10	39

* See Spiro and coworkers[34] for staging system.
† Some patients had more than one site of failure; 26 patients excluded from analysis (see Spiro and coworkers[34]).
‡ All but two had local recurrence also.
§ Local disease controlled in 13 patients.
(Spiro RH, Huvos AG, Strong EW. Cancer of the parotid gland: a clinicopathologic study of 288 primary cases. Am J Surg 1975;130:457)

previously untreated malignant tumors. The incidence of clinically positive lymph nodes on admission, in patients with high-grade tumors, was 19%; the incidence of subclinical disease after elective neck dissection was 8%; an additional 8% later developed metastatic disease in the neck. The overall risk for neck disease in patients with high-grade carcinomas was, therefore, 35%. Curative resection was attempted in 264 patients; only 12 patients received postoperative radiation therapy. The sites of recurrence by stage are shown in Table 27-3. Local recurrence was recorded in 27% of cases. All but two of the patients with neck failure also had recurrence at the primary site. The local recurrence rate for mobile, solitary lesions 1 to 3 cm in size (stage I) was only 7%. The recurrence rate increased to 21% for 3- to 6-cm masses (stage II), which may be mobile or partially fixed. The advanced lesions (stage III), which were almost all high-grade lesions, were larger than 6 cm, or had multiple tumor masses, ulceration, deep fixation, facial nerve palsy, or clinically positive lymph nodes, had a 58% rate of local failure. Thirty-four patients were treated for recurrent disease, and in 15 the disease was controlled. Prognostic factors are listed in Table 27-4. Low histologic grade and early stage promised a better prognosis, but the site of origin within the gland (ie, body, tail, or deep lobe) was irrelevant to prognosis.

Guillamondegui and colleagues[18] reported the results from the M.D. Anderson Hospital for 120 previously untreated malignant tumors of the parotid that were treated between 1944 and 1965. The period of observation ranged from 7 to 28 years. Surgery was the initial treatment in 104 patients, surgery and postoperative radiotherapy in 10 patients, and radiotherapy in 6 patients. The local recurrence rate after surgery alone was 8% for 38 low-grade tumors, and all three failures were controlled. The local recurrence rate after surgery alone was 35% for 66 high-grade carcinomas; three of the recurrences were controlled with subsequent treatment for an ultimate local failure rate of 30%. The absolute 5-year survival rate according to histologic type is shown in Table 27-5.

McNaney and coworkers[24] reported the M.D. Anderson Hospital experience for 77 patients with malignant parotid tumors who received postoperative radiation

TABLE 27-4. Malignant Tumors of the Parotid: Factors Affecting 5-Year Absolute Cure Rate (288 Patients)

Factor	Patients	No Evidence of Disease at 5 Y (%)
Facial nerve intact	212	66
Nerve palsy	43	14
Tumor spill	32	58
No tumor spill	256	50
Neck negative (N0)	157	74
Neck positive (N+) on admission	57	9
Neck pasitive (N+) delayed	18	17
No local recurrence	194	79
Local recurrence	71	21

Note: Memorial Sloan-Kettering data; patients treated 1939 to 1968. (Modified from Spiro RH, Huvos AG, Strong EW. Cancer of the parotid gland: a clinicopathologic study of 288 cases. Am J Surg 1975;130:458)

TABLE 27-5. Parotid Cancer: Absolute 5-Year Survival (120 Patients)

Histologic Type	Patients	5-Y Survival (%)
Acinic cell	12	92
Mucoepidermoid (low grade)	28	76
Adenocarcinoma	12	66
Malignant mixed	27	50
Adenoid cystic	10	50
Squamous cell	6	50
Mucoepidermoid (high grade)	13	46
Undifferentiated	12	33

Note: M.D. Anderson Hospital data; patients treated 1944 to 1965. (Guillamondegui OM, Byers RM, Luna MA, Chiminazzo H Jr, Jesse RH, Fletcher GH. Aggressive surgery in treatment for parotid cancer: the role of adjunctive postoperative radiotherapy. Am J Roentgenol Radium Ther Nucl Med 1975;123:50. Copyright © 1975, American Roentgen Ray Society)

TABLE 27-6. Postoperative Radiation Therapy in Malignant Tumors of the Parotid Gland: Local–Regional Failures by Extent of Residual Disease

		Site of Failure		
Residual Disease	Patients	Primary Site	Neck	Primary Site and Neck
Gross (any grade)	14	1	1	0
Microscopic (any grade)	26	2	1	0
High grade (good margin)	16	1	2	0
Unknown grade (good margin)	17	1	0	1
Low grade (questionable margin)	4	0	0	0
TOTAL	77	5	4	1

(Adapted from McNaney D, McNeese MD, Guillamondegui OM, Fletcher GH, Oswald MJ. Postoperative irradiation in malignant epithelial tumors of the parotid. Int J Radiat Oncol Biol Phys 1983;9:1294. Copyright © 1983, Pergamon Press, Ltd.)

therapy. Parotidectomy was performed for a previously untreated tumor in 54 patients (70%) and for a recurrent tumor in 23 patients (30%). Patients with a history of more than two surgical procedures for parotid tumor were excluded. Minimum follow-up was 3 years; follow-up was greater than 5 years in 81% and greater than 10 years in 27% of patients. The sites of local–regional failures are shown in Table 27-6 according to the estimated extent of residual disease after parotidectomy. The overall incidence of local failure was 8% (6 of 77), and the incidence of neck failure alone was 5% (4 of 77). No failures have occurred more than 4 years after treatment. No local or regional failures occurred in the 14 patients with low-grade lesions. The parotid bed failure rate for high-grade tumors was 10% (6 of 63). Analysis of local recurrence according to the extent of facial nerve sacrifice showed one local failure in 21 cases after partial facial nerve resection, and three local failures in 21 cases after total resection of the nerve. Distant metastases developed in 18 patients (23%).

Black and coworkers[8] reviewed the results of 62 cases of adenoid cystic carcinoma managed at the Princess Margaret Hospital (Toronto) between 1957 and 1974. Fifty cases were in major salivary glands and 12 were in minor salivary glands. Ten percent had clinically positive lymph node results on admission, and another 10% subsequently developed positive lymph node findings. The results by method of treatment are shown in Table 27-7. The postoperative dose was 5000 cGy over 4 weeks. The actuarial 5- and 10-year survival rates were 78% and 57%, respectively. The 10-year survival rate with lesions less than 3 cm was 73% and for those greater than 3 cm, 38%. The lesions in all six survivors treated by surgery alone were less than 3 cm. Twenty-three patients developed pulmonary metastasis. Eleven survived for 3 years, and one is asymptomatic after 7 years. Six patients were treated by chemotherapy without objective response.

Tapley[36] reported the M.D. Anderson Hospital results for 13 unresectable malignant parotid tumors treated by radiation therapy. Only three patients were observed to develop local recurrence, but eight developed distant metastases. A single patient was alive, free of disease, at 5 years. Tapley also analyzed 38 patients treated by radiation therapy for recurrent disease after initial surgery. Twenty-four percent developed local recurrence. Eight patients (21%) were living, free of disease, for 3 to 20 years.

Submandibular Gland

Weber and associates[37] reviewed the M.D. Anderson Hospital 41-year experience for 24 benign and 86 malignant tumors.

The benign tumors were managed by surgery and no recurrences appeared.

The malignant lesions presented with a variety of

TABLE 27-7. Adenoid Cystic Carcinoma

Initial Therapy	Patients*	Persistence After Therapy	Local Recurrence	Salvage (Surgery + Radiotherapy)	Neck Recurrence With Primary Lesion Controlled	Distant Metastases	No Evidence of Disease (5–20 Y)
Surgery	19	2	11/17	5	0	0	6
Surgery + radiotherapy	35	0	6	0	2	4	23
Radiotherapy	8	3	4/5	0	1†	No data	0

* Major salivary glands, 50 cases; minor salivary glands, 12 cases.

† Salvage by surgery and radiotherapy.

Note: Princess Margaret Hospital data, Toronto.

(Modified from Black KM, Fitzpatrick PJ, Palmer JA. Adenoid cystic carcinoma of the salivary glands. Can J Surg 1980;23:34)

TABLE 27-8. Submandibular Gland Carcinoma: Results of Treatment

Clinical Situation	Patients	Local–Regional Recurrence	Distant Metastasis
No prior treatment			
Surgery alone	19	7	2
Surgery + radiotherapy	2	0	2
Excisional biopsy			
Radiotherapy	9	1	1
Excisional biopsy: recurrent cancer present			
Surgery	19	3	1
Surgery + radiotherapy	18	1	6
Incisional biopsy			
Surgery	9	3	0
Radiotherapy	1	0	1
Surgery + radiotherapy	8	2	2
Regional dissection: no gross disease present			
Radiotherapy	5	1	2
Surgery + radiotherapy	2	2	0
Biopsy + radiotherapy: recurrent cancer present			
Surgery	3	1	1
Surgery + radiotherapy	1	0	0

Note: M.D. Anderson Hospital data; patients treated 1944 to 1985.
(Data from Weber and coworkers.[37])

clinical situations: no prior treatment (21), excisional treatment (30), incisional treatment (18), neck dissection (7), or recurrence after biopsy and radiation therapy (4). The local–regional control rate was improved with postoperative radiation therapy, especially if soft tissue extension was present. The local–regional control rate and incidence of distant metastasis according to the clinical situation and treatment plan are shown in Table 27-8. Local–regional recurrence in patients with perineural invasion was 38% with surgery alone (13 patients) compared with 8% for combined treatment (24 patients). Histologic features, size, and perineural invasion did not affect overall survival. The presence of soft tissue extension outside the gland and lymph node metastasis were adverse prognostic features. The 5-year cause-specific survival rate was 69%, and the 10-year rate was about 59%. For stages T1 through T4A, the 5-year cause-specific survival rate was 88%, compared with 55% for T4B. The 5-year survival rate was 86% when lymph nodes contained no tumor, and 30% when they contained tumor.

FOLLOW-UP POLICY

Late recurrences develop in the benign mixed tumors, acinic cell carcinoma, and adenoid cystic carcinoma, requiring lifetime follow-up. Neurologic symptoms or signs in the absence of physical findings of recurrent disease often are the harbinger of perineural recurrence.

Benign Mixed Tumors

Magnetic resonance imaging is the preferred method of confirming the clinical impression of recurrent tumor. T2-weighted or fat-suppressed MRI often will clearly show the difference between postoperative, end-stage fibrosis and recurrent tumor nodules. Tumor nodules are usually bright (see Chap. 4).

Malignant Tumors

If tumor spill or incomplete excision is suspected after surgery, baseline MRI may be obtained about 6 weeks after surgery. Persistent areas of increased signal intensity on T2-weighted or fat-suppressed images in the operative bed should be followed up carefully and considered suggestive of recurrent tumor.

Recurrent malignant tumors often are much more extensive than can be appreciated on physical examination. Imaging studies will frequently show perineural spread or spread to the skull base, which may be considered inoperable. Both CT and MRI are usually required for evaluation of recurrent disease adjacent to the skull base (see Chapter 4).

COMPLICATIONS OF TREATMENT

Surgical Treatment

Benign Mixed Tumors

Gleave and coworkers reported the operative complications for 369 new and 103 recurrent benign mixed tumors of the parotid gland[17] (Table 27-9). Postoperative irradiation was used in 13% of new cases and 41% of recurrent cases. Amputation neuromas occur in 5% to 10% of cases, but they seldom require excision unless constant irritation from clothing causes symptoms.

Malignant Tumors

Loss of sensation in the ear lobe after surgical treatment of a malignant tumor is a minor annoyance, particularly to women.

Gustatory sweating (Frey's syndrome) occurs in 5% to 25% of patients after parotidectomy, but it can be reduced by cutting thicker skin flaps.[33] This problem un-

TABLE 27-9. Morbidity After Treatment of Benign Mixed Tumors of the Parotid

Disorder	Rate (%)	
	New BMT (369 Cases)	Recurrent BMT (103 Cases)
Facial nerve paresis		
Temporary	15	21.4
Permanent	1.3	12.6
Frey's syndrome	11.1	28
Amputation neuroma	5.7	9.7
Salivary fistula	0.2	1.9
Radiation-induced malignancy	0	0.97

BMT, benign mixed tumors.
(Adapted from Gleave EN, Whittaker JS, Nicholson A. Salivary tumors: experience over 30 years. Clin Otolaryngol 1979;4:251–252)

commonly requires treatment, but it can sometimes be managed with a topical application of scopolamine. Symptoms usually decrease with time. Tympanic neurectomy is reasonably successful in controlling the syndrome when it is sufficiently annoying.

Temporary paresis of the facial nerve occurs in about 50% of uncomplicated lateral lobectomies because of intraoperative manipulation. Some degree of paresis may be expected in nearly all parotidectomies performed for more complicated problems. Recovery normally occurs in 1 to 6 months; it is unknown whether postoperative radiation therapy slows recovery, but we have observed gradual recovery of nerve function even during the course of irradiation.

If complete paralysis occurs unexpectedly in the immediate postoperative period, it may be necessary to reexplore the nerve to exclude the possibility that the nerve was inadvertently severed or ligated, and if so, to repair the nerve immediately. If one or more branches or the main trunk has been resected, a decision must be made regarding immediate grafting. If postoperative radiation therapy is not to be added, then immediate nerve graft usually is preferred. If postoperative radiation therapy is to be added, however, opinion is mixed as to the likelihood of success.[11,12,22,23,28]

Pillsbury and Fisch[28] studied nine patients treated by facial nerve graft and postoperative radiation therapy. Facial movements were reduced from an average of 70% of normal without radiation therapy to 25% of normal. They recommend the use of fascia lata slings and muscle transfer to restore facial symmetry as an alternative to nerve grafting when irradiation is recommended. If nerve grafting has been done, it would seem prudent to wait as long as is practical before starting the radiation therapy.

Little experience has been reported with delayed nerve grafting after postoperative irradiation. Delayed nerve grafting is difficult even in unirradiated patients owing to scarring in the surgical bed, and the additional fibrosis incurred by radiation therapy would make it nearly impossible.

A few cases have been reported of return of facial movement without grafting after complete resection of the trunk of the facial nerve.[12]

Radiation Therapy

Xerostomia usually is avoided by techniques that spare the contralateral salivary tissues, but it occurs to a moderate degree in some cases, even with doses to the contralateral salivary tissues of 3000 cGy or less.

Trismus may occur due to fibrosis of the masseter and pterygoid muscles. The temporomandibular joint almost always receives a high dose, but seldom develops symptomatic ankylosis.

Serous otitis media may occur, and a dry ear canal occurs in nearly all cases. Localized hair loss may occur with some techniques.

Radiation damage to the facial nerve has not been observed even with doses in the range of 8000 to 9000 cGy; however, other motor nerves have shown late-onset radiation-induced neuropathy, and presumably the facial nerve is not immune to this risk. Brain stem injuries and temporal lobe necrosis have been reported (see Chap. 13).

Bone exposure and osteoradionecrosis of the external auditory canal are reported. Osteoradionecrosis of the mandible is infrequent.

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28

MINOR SALIVARY GLAND TUMORS

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Tumors of minor salivary gland origin are uncommon, accounting for 2% to 3% of all malignant neoplasms of the upper aerodigestive tract. They may appear at any age, but their presentation is uncommon before age 20 and rare under age 10. They occur most often in the oral cavity, nasal cavity, and paranasal sinuses. Thus, the site of origin is related more to the population density of the minor salivary glands in a particular tissue than to any environmental factor. The adenocarcinomas of the nasal cavity are reported to be associated with certain occupations (see Chap. 22).

ANATOMY

Minor salivary glands are ubiquitous in the mucosa of the upper aerodigestive tract, with the exception of the gingivae and the anterior portion of the hard palate, in which they are absent. The glands are distributed on the undersurface of the anterior and lateral oral tongue and on the base of the tongue. Aberrant salivary tissue is sometimes seen in lymph nodes, in the body of the mandible just behind the third molar teeth, in the vestigial remnant of the nasopalatine canal that lies in the anterior maxilla, in the middle ear, in the lower neck, in the sternoclavicular joint, in the thyroglossal duct, and at other sites.

PATHOLOGY

Approximately one half of minor salivary gland tumors are malignant. The histologic varieties of malignant tumors include adenoid cystic carcinoma, mucoepidermoid carcinoma, adenocarcinoma, and malignant mixed, acinic cell, and oncocytic carcinomas. About two thirds of the malignant tumors are adenoid cystic. The mucoepidermoid carcinoma and adenocarcinoma arise predominantly in the oral cavity (Schell S, Barkley HT Jr, Chiminazzo H Jr. Malignant tumors of minor salivary glands, unpublished study, 1983) (Table 28-1).

The great majority of benign tumors are benign mixed tumors (Fig. 28-1) with a sprinkling of intraductal papillomas, papillary cystadenomas, basal cell adenomas,[14] and benign oncocytomas.

PATTERNS OF SPREAD

Primary Site

The sites of origin for minor salivary gland tumors in 118 patients are listed in Table 28-1. Tongue lesions usually originate from the base of the tongue. There are no minor salivary glands in the anterior one half or the midline of the hard palate, so tumors arise on the posterolateral hard palate and all of the soft palate. The site of origin for salivary gland tumors of the floor of the mouth is moot—either the sublingual gland or a minor salivary gland. These tumors grow by extensive local infiltration with eventual invasion of muscle, bone, cartilage, nerves, and blood vessels. Perineural spread is diagnosed histologically in about 50% of adenoid cystic carcinomas. The tumor may track both centrally and peripherally along nerves, but the central spread is the more common event because most lesions arise near the terminations of the nerves. Extension along nerves eventually may traverse the base of the skull and present intracranially, although this spread pattern may not be recognized for several years after the original treatment. Tumor growth along a nerve may be characterized by skipped areas, so that a normal nerve segment is no assurance of free margins. Adenoid cystic carcinoma may grow along the haversian systems of bone without showing bone destruction.[11]

TABLE 28-1. Site of Presentation and Histology for 118 Malignant Minor Salivary Gland Tumors

Site	Patients	Adenoid Cystic	Mucoepidermoid		Adenocarcinoma	Malignant Mixed	Acinic Cell
			High Grade	Low Grade			
Lip	2	1	0	0	1	0	0
Buccal mucosa	16	9	1	3	3	0	0
Tongue	17	10	2	1	4	0	0
Floor of mouth	22	10	4	3	4	0	1
Gingivae	13	3	5	1	4	0	0
Palate	23	15	1	3	4	0	0
Paranasal sinuses and nasal cavity	20	16	1	1	2	0	0
Nasopharynx and pharynx	3	1	0	1	0	1	0
Trachea	1	1	0	0	0	0	0
Larynx	1	1	0	0	0	0	0
TOTAL	118	67	14	13	22	1	1

Note: M.D. Anderson Hospital data; patients treated January 1970 through February 1978.
(Data from unpublished study by Schell S, Barkley HT Jr, Chiminazzo H Jr. Treatment of malignant minor salivary gland tumors. 1983)

Lymphatic Spread

The risk for lymph node metastases is related to the site of origin and the grade of the tumor. Lymph node metastases are most likely from sites with a dense capillary lymphatic network (eg, nasopharynx, tonsillar fossa, base of the tongue). The incidence of lymph node metastasis was 59% (10 of 17) in patients with oropharynx or nasopharynx primaries and predictably low for the hard palate, 7% (1 of 14), and paranasal sinuses, 6% (2 of 34).[10] The patterns of spread are similar to those for squamous cell carcinoma.

Low-grade mucoepidermoid and acinic cell carcinomas are at low risk to spread to lymph nodes. Approximately 20% of adenoid cystic carcinomas spread to lymph nodes, but this low incidence is partly related to their frequent site of origin in the hard palate and paranasal sinuses, areas that infrequently produce lymph node metastases. The high-grade tumors (high-grade mucoepidermoid carcinoma, adenocarcinoma, and malignant mixed tumor) have approximately a 30% incidence of lymph node involvement on admission, and eventually 51% showed lymph node metastases.[10] Schell and coworkers found a 17% incidence of positive nodes on admission for all histologies and grades and subsequent appearance in 11% (Schell S, Barkley HT Jr, Chiminazzo H Jr. Malignant tumors of minor salivary glands, unpublished study, 1983). Most were staged N1 or N2a and were usually associated with lesions of the tongue or floor of the mouth.

Figure 28-1. Benign mixed tumor of hard palate. The patient was elderly and elected no treatment.

Distant Metastasis

At least 25% of patients develop distant metastasis, and the rate for adenoid cystic carcinoma is closer to 50%. The lung is the site first recognized, but no site is exempt.

CLINICAL PICTURE

The clinical picture depends on the site of origin and the histology. Benign tumors grow slowly, usually as an asymptomatic submucosal mass. As they increase in size, they usually produce minor symptoms related to the mass and eventually may ulcerate, erode bone, or cause obstruction. The signs and symptoms of malignant

tumors differ somewhat from those of squamous cell carcinoma arising from the same anatomic area. Many of the lesions are indolent, and the history may go back many months or even years; about 25% give a history of a mass being present over 10 years. Because the lesions develop under the epithelium, the initial lesion is a submucosal mass that is often painless until ulceration develops. Perineural involvement is expressed as pain, nerve palsies, or paresthesias; the neurologic syndromes may be perplexing and difficult to reconcile with the gross extent of disease as determined by physical examination and roentgenographic examination. There is often a delay of several months during which the symptoms remain unexplained in the face of normal computed tomography (CT) or magnetic resonance imaging (MRI) and minimal neurologic findings. Persistent unexplained neurologic symptoms should be considered prima facie evidence of perineural spread beyond the site of origin. Otherwise, the clinical picture resembles that for squamous cell carcinomas for a given size and site. Lymph node metastases occur at predictable sites. The clinically positive nodes are usually small and mobile, but a neck dissection on such a patient may show numerous small, clinically undetectable positive nodes, particularly in the case of adenoid cystic carcinoma.

METHODS OF DIAGNOSIS AND STAGING

The differential diagnosis includes lesions that produce an enlarging submucosal mass, such as an abscess, a stone in a duct, a cyst of soft tissue or bone, a sarcoma, or a lymphoma.

Because of the infrequency of these lesions, faulty histologic interpretation is not unusual and often leads to inappropriate therapy.

The staging systems applied to squamous cell carcinomas may be used, although few reported series bother to correlate size and extent of tumor with results by various treatment modalities. Imaging studies are similar to those used for squamous cell carcinomas for a specific site. Studies to rule out metastases are usually limited to a chest roentgenogram.

TREATMENT

Selection of Treatment Modality

Surgery and irradiation are the only curative therapies available. There is little disagreement about the value of operation, but there remains considerable disagreement regarding the results of irradiation.

Most series reporting poor results from radiation therapy mention neither the selection of patients for irradiation nor the doses and volumes used. Because radiation therapy has often been used as a last-ditch effort for high-grade, advanced lesions after multiple surgical procedures, it is hardly surprising that results in some reports have been poor. Those series using radiation therapy alone for early lesions or as an immediate postoperative adjunct to surgical removal have had a favorable experience. After all, the histologies of the minor salivary gland tumors are the same as those of parotid gland tumors, and it is generally accepted that routine postoperative irradiation decreases the local recurrence rate in high-grade parotid lesions and that irradiation alone even controls a few locally recurrent or inoperable parotid tumors.[6] The response of malignant minor salivary gland tumors to irradiation is generally similar to that of a squamous cell carcinoma of the same size and same anatomic site, and the doses used are similar.

Low-Grade Tumors

The low-grade lesions (ie, low-grade mucoepidermoid carcinoma, acinic cell carcinoma, and benign mixed tumors) are treated initially by an operation when feasible, but radiotherapy is sometimes used as the initial primary treatment for inaccessible lesions (eg, nasopharynx, sphenoid sinus) or when the functional loss would be considerable (Fig. 28-2). If there is failure to respond to radiotherapy, the treatment is discontinued and operation is advised (Fig. 28-3). Postoperative irradiation is added for close margins or for those lesions that have recurred more than once. If the patient presents after excisional biopsy of a small lesion, irradiation is an alternative to reexcision, particularly if the procedure would produce significant cosmetic or functional loss.

The benign mixed tumors respond to radiation therapy, although complete regression is unusual. Long-term cure by radiation therapy alone has been reported. Surgery, however, remains the treatment of choice, and the major use of radiation therapy has been as an adjunct to operation in cases at significant risk for recurrence. The benign mixed tumors of minor salivary gland origin are reputed to be more radiosensitive than those arising in the parotid gland, but this may be a function of tumor volume rather than of inherent differences in radiosensitivity.

High-Grade Tumors

The treatment of high-grade lesions (adenocarcinomas, high-grade mucoepidermoid and malignant mixed tumors) varies immensely, depending on the site of origin, stage of disease, and willingness of the patient to accept a major cosmetic or functional change subsequent to an operation. Our approach is to accept radiation therapy as a curative therapy, and we essentially approach most lesions as we would a squamous cell carcinoma of similar stage and similar anatomic site. Surgical excision and postoperative irradiation is a common treatment plan for the advanced lesions that are resectable. Early lesions may be selected for radiation therapy alone or surgery and postoperative radiation therapy. We have no experience with radiation therapy alone for malignant mixed tumors and would select surgery as the main treatment option.

Adenoid Cystic Carcinoma

The management of adenoid cystic carcinomas is often a frustrating experience. Histologically, they appear low grade, but biologically they are high grade in the sense that they are difficult to cure because of their insidious growth pattern and tendency to develop late recurrences and a high rate of distant metastases. Treatment is individualized based on anatomic site, tumor size, and age of the patient. Early lesions (American Joint Committee on Cancer [AJCC] stage I or II) may be managed

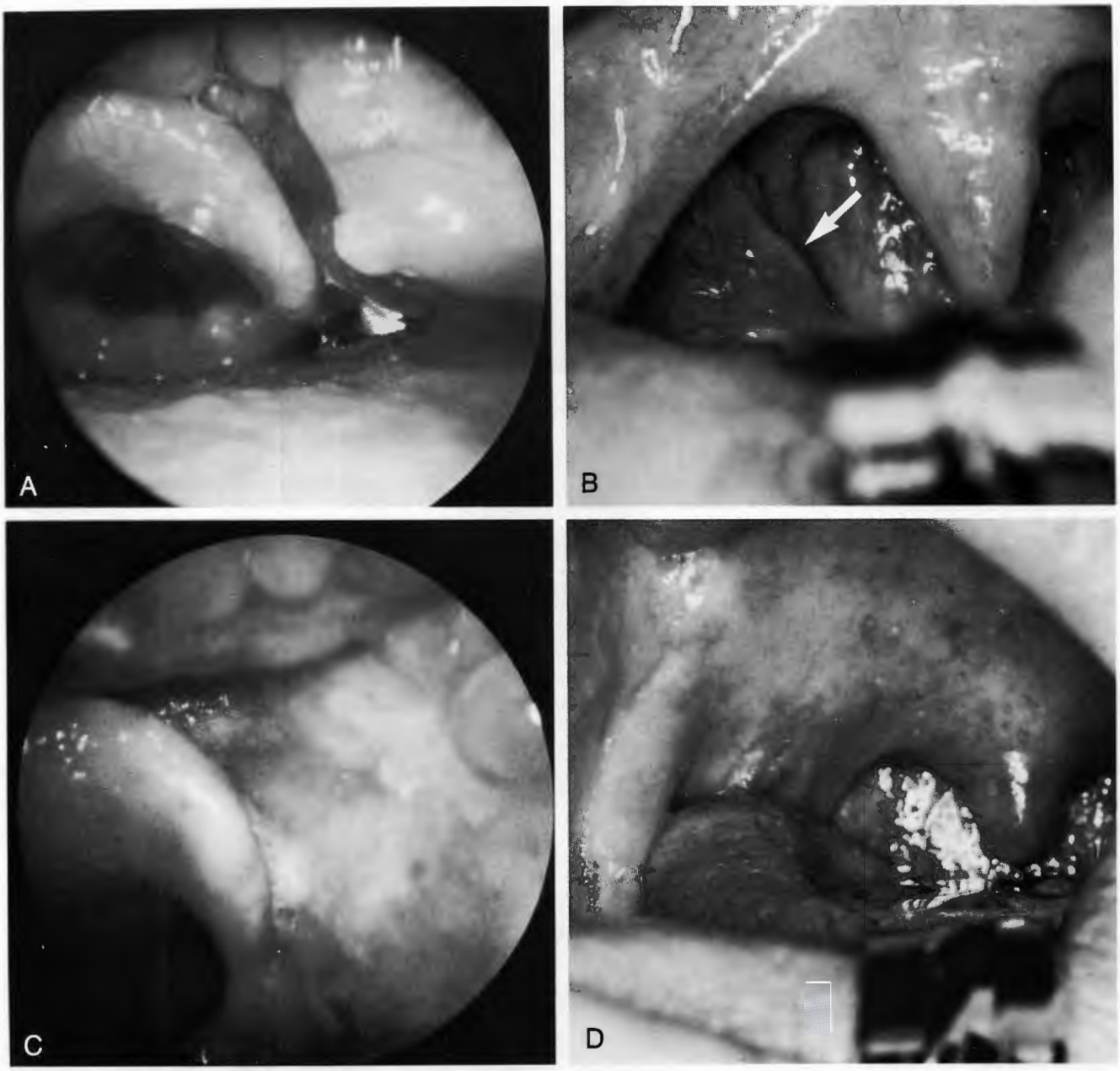

Figure 28-2. A 71-year-old woman presented with a 4-month history of lump in the right side of her throat (for color photographs, see Color Fig. 9*C* and *D* in Chap. 3). (*A*) There was a 4 × 5-cm submucosal lesion in the right base of the tongue extending to the vallecula. (*B*) Extension of submucosal tumor mass into right tonsillar fossa. Neck was negative. Biopsy showed mucoepidermoid carcinoma, low grade. Treatment plan was 7500 cGy tumor dose over 8½ weeks, ^{60}Co. There was 70% regression at completion of treatment. (*C* and *D*) There was complete disappearance of tumor at 5 months. (Patient was free of disease at 27 months when she died of disseminated bladder cancer.)

by radiation therapy alone or excision and reevaluation for postoperative radiation therapy. The surgeon is often in a quandary regarding the amount of tissue to resect because of the proclivity for perineural spread; the tumor margins are frequently positive even after a generous resection. Postoperative radiation therapy would be considered for a clinically positive margin or perineural invasion; the age of the patient—quite young or quite old—may advise observation. Likewise, if the irradiation portals will jeopardize vision, observation may be selected.

Advanced lesions (stage III and IV) are usually best managed by resection and postoperative radiation therapy. The surgical procedure should attempt tumor-free margins, but extensive resections of normal structures and nerves are not usually indicated, and radiotherapy is used to control any peripheral spread.

Lesions with extensive bone destruction or perineural

invasion may be treated with high-dose palliative radiotherapy. Adenoid cystic carcinomas are generally radiosensitive, and even large lesions often disappear. A typical response for primary adenoid cystic carcinoma of the palate treated by radiotherapy alone is shown in Figures 28-4 through 28-6.[8] If the lesion fails to disappear, surgical excision follows immediately (Fig. 28-7). However, eventually, most advanced lesions recur after several years of apparent healing. Our approach has sometimes been to use radiation therapy as the initial treatment, reserving operation for radiation therapy failure. This gives the patient several years without the functional loss from the operation. The opposite tack may be chosen in which operation is used initially and radiation therapy is reserved for recurrence. There is no evidence that any one sequence of therapies is best, and, therefore, each case is individualized. In some cases, combined therapy may be used from the outset.

When combined treatment is indicated, the operation should precede radiation therapy to facilitate healing and gain knowledge of tumor extent for radiation treatment planning.

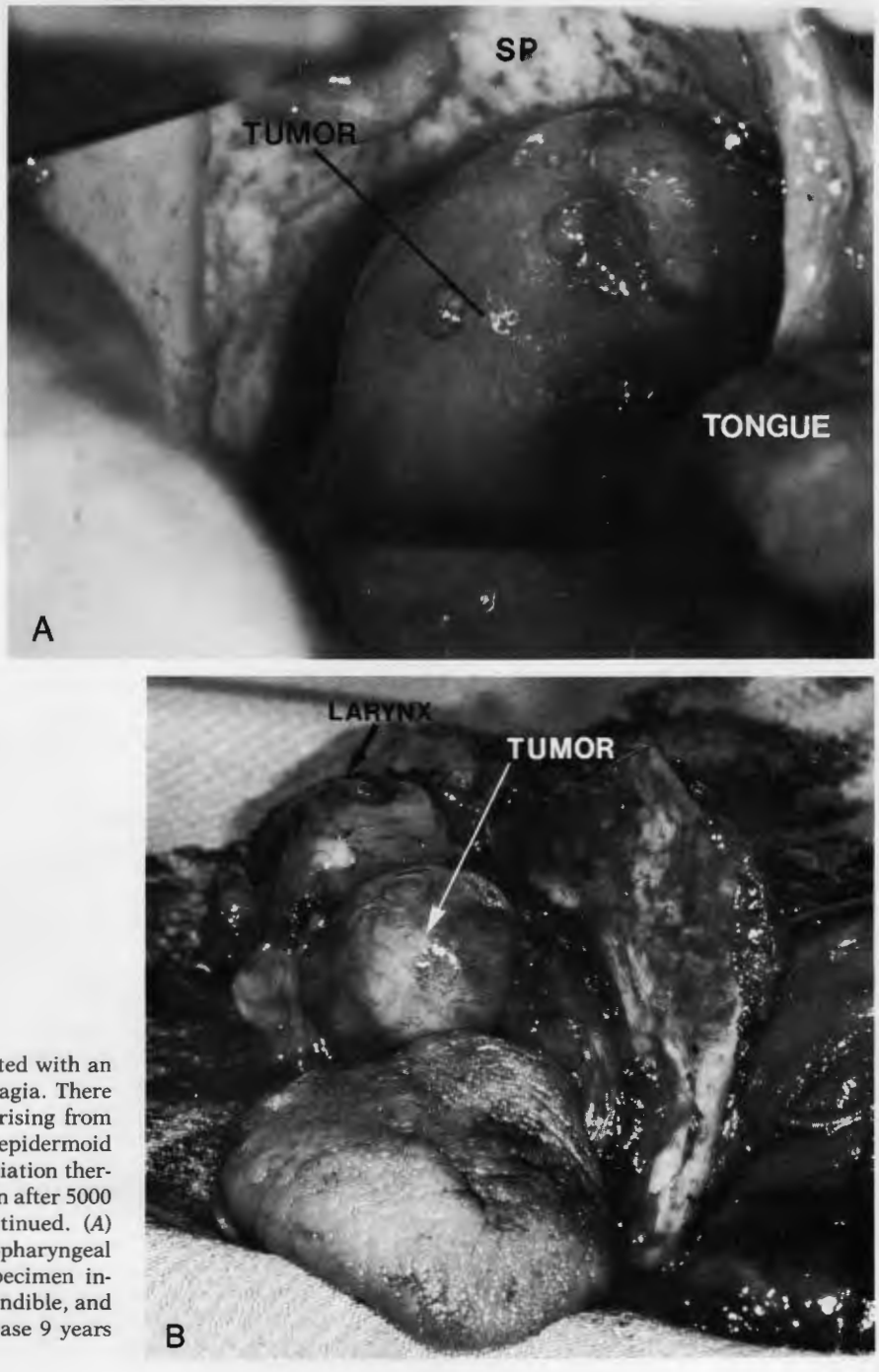

Figure 28-3. A 52-year-old man presented with an 8-month history of hoarseness and dysphagia. There was a huge submucosal mass probably arising from the left vallecula. Biopsy showed mucoepidermoid carcinoma. The patient was started on radiation therapy, but there had been only 25% regression after 5000 cGy, and radiation therapy was discontinued. (*A*) Large submucosal mass occluded the oropharyngeal aperture. SP, soft palate. (*B*) Surgical specimen including the entire tongue, larynx, hemimandible, and neck specimen. The patient is free of disease 9 years after treatment.

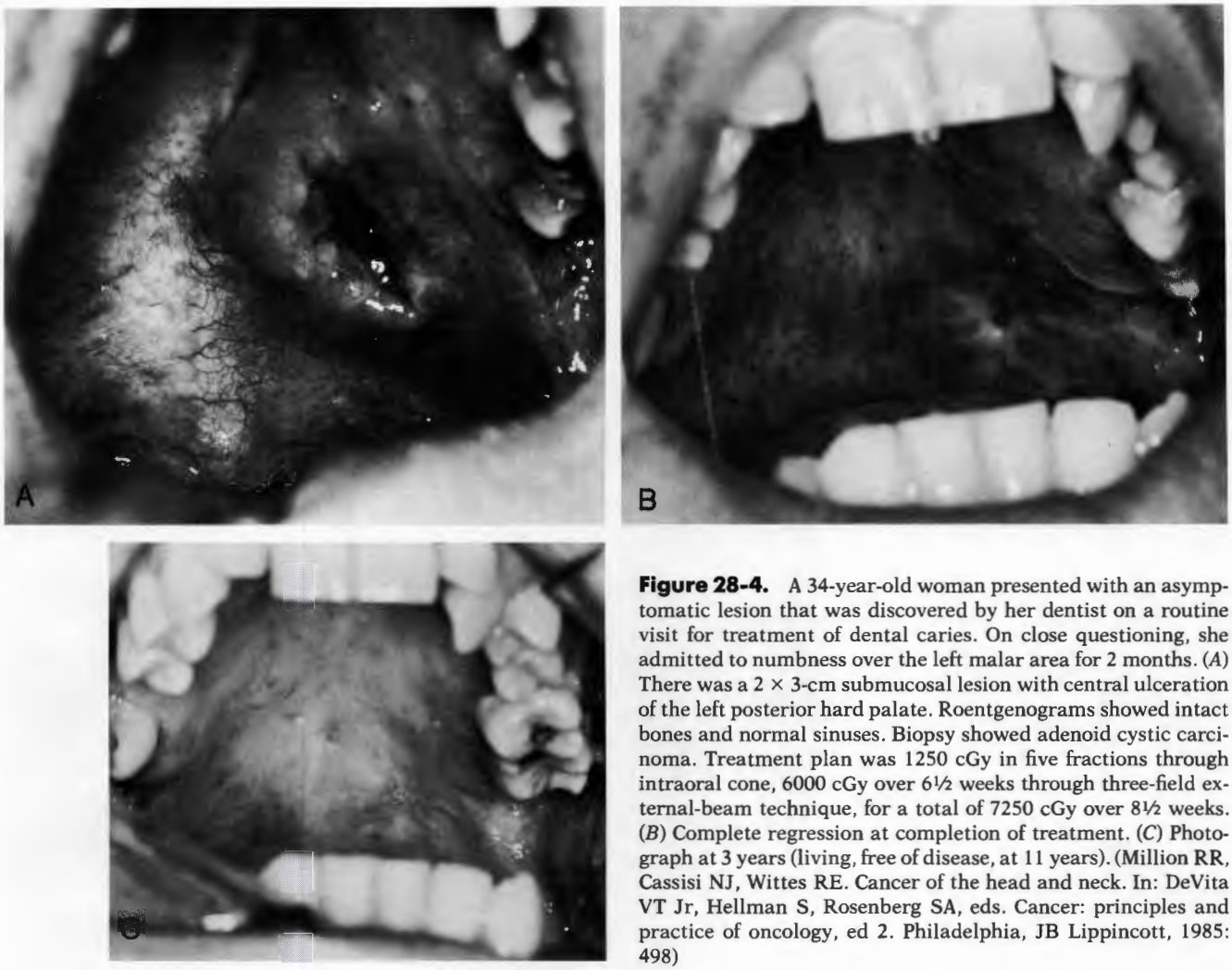

Figure 28-4. A 34-year-old woman presented with an asymptomatic lesion that was discovered by her dentist on a routine visit for treatment of dental caries. On close questioning, she admitted to numbness over the left malar area for 2 months. (*A*) There was a 2 × 3-cm submucosal lesion with central ulceration of the left posterior hard palate. Roentgenograms showed intact bones and normal sinuses. Biopsy showed adenoid cystic carcinoma. Treatment plan was 1250 cGy in five fractions through intraoral cone, 6000 cGy over 6½ weeks through three-field external-beam technique, for a total of 7250 cGy over 8½ weeks. (*B*) Complete regression at completion of treatment. (*C*) Photograph at 3 years (living, free of disease, at 11 years). (Million RR, Cassisi NJ, Wittes RE. Cancer of the head and neck. In: DeVita VT Jr, Hellman S, Rosenberg SA, eds. Cancer: principles and practice of oncology, ed 2. Philadelphia, JB Lippincott, 1985: 498)

Chemotherapy

Because of the rarity of these neoplasms, information about chemotherapy is almost entirely anecdotal. Some evidence of antitumor effects has been seen with 5-fluorouracil, hydroxyurea, methotrexate, and cisplatin with bleomycin,[9,12,15,18] but the magnitudes of responses are often difficult to evaluate in the context of broad phase II studies or retrospective reviews of medical records. Using a combination of methyl-CCNU, doxorubicin (Adriamycin), and vincristine, Hayes and coworkers[5] reported significant responses in adenoid cystic carcinoma.

Surgical Treatment

Benign tumors are removed by wide local excision that includes a cuff of normal tissue. Enucleation is insufficient owing to the high recurrence rate.

For malignant lesions, the surgical approach is dictated by the histology and anatomic site. Small low-grade lesions may be removed with a wide local excision including a shell of normal tissue. Large low-grade lesions and high-grade lesions require a radical resection, which would be similar to that used for a squamous cell carcinoma of the same location and extent. Elective neck dissection is not often advised. Postoperative radiation therapy is often recommended. Resection of adenoid cystic carcinoma must allow for propensity for perineural and direct extension far beyond the gross lesion. It is not possible, of course, to remove all the nerves potentially involved, but nerves grossly involved should be sacrificed wherever reasonable to do so. As an alternative, postoperative irradiation may be used to cover the perineural routes of spread. Because unsuccessfully treated patients often live many years before they eventually die of their disease, careful planning must go into reconstruction and rehabilitation.

Irradiation Technique

The irradiation techniques are similar to those for squamous cell carcinomas of the same anatomic site and similar tumor size, with the exception that nerve pathways are covered for adenoid cystic carcinomas and other histologies with nerve involvement. Recurrences are fre-

quently manifested in and about the base of the skull at the origin of the cranial nerves.

Dose and fractionation schedules are similar to those used for squamous cell carcinomas except for adenoid cystic carcinomas. A time–dose analysis for localized adenoid cystic carcinoma showed long-term local control only in lesions receiving 7000 cGy or greater in 8 weeks or less when radiation therapy alone was used. When radiation therapy was used in conjunction with operation, a dose of 6500 cGy or greater was needed for a high local control rate.[4]

The regression rate of adenoid cystic carcinoma during treatment is similar to that of squamous cell carcinoma. Successfully treated adenocarcinomas or low-grade mucoepidermoid carcinomas may require several weeks or months to disappear after completion of treatment. The regional lymphatics are electively irradiated depending on the site of origin and the grade of the lesion.

The response of benign mixed tumors is predictably slow and often incomplete.

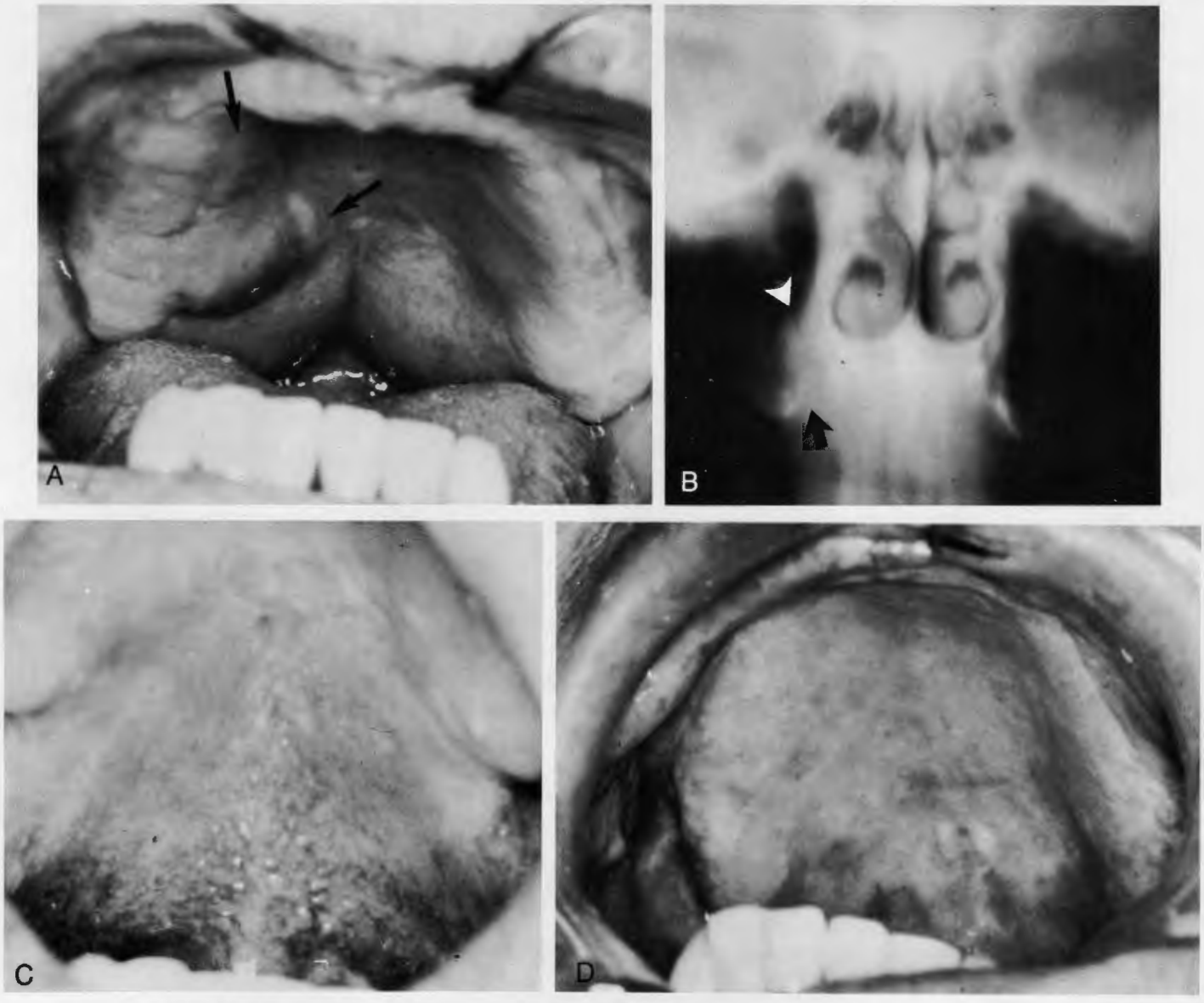

Figure 28-5. (*A*) Adenoid cystic carcinoma of the right maxillary sinus with destruction of maxilla and tumor present submucosally in right hard palate (*arrows*). (*B*) Coronal tomogram shows mass in maxillary antrum (*arrowhead*) and bone destruction of floor of the sinus (*arrow*). The patient refused operation. Treatment plan was 7000 cGy over 7 weeks, ^{60}Co, three fields (anterior and right and left lateral). The eyes were shielded. There was complete disappearance of the submucosal mass at completion of therapy. (*C*) Appearance at 1 month. (*D*) There was no evidence of disease at 9 years.

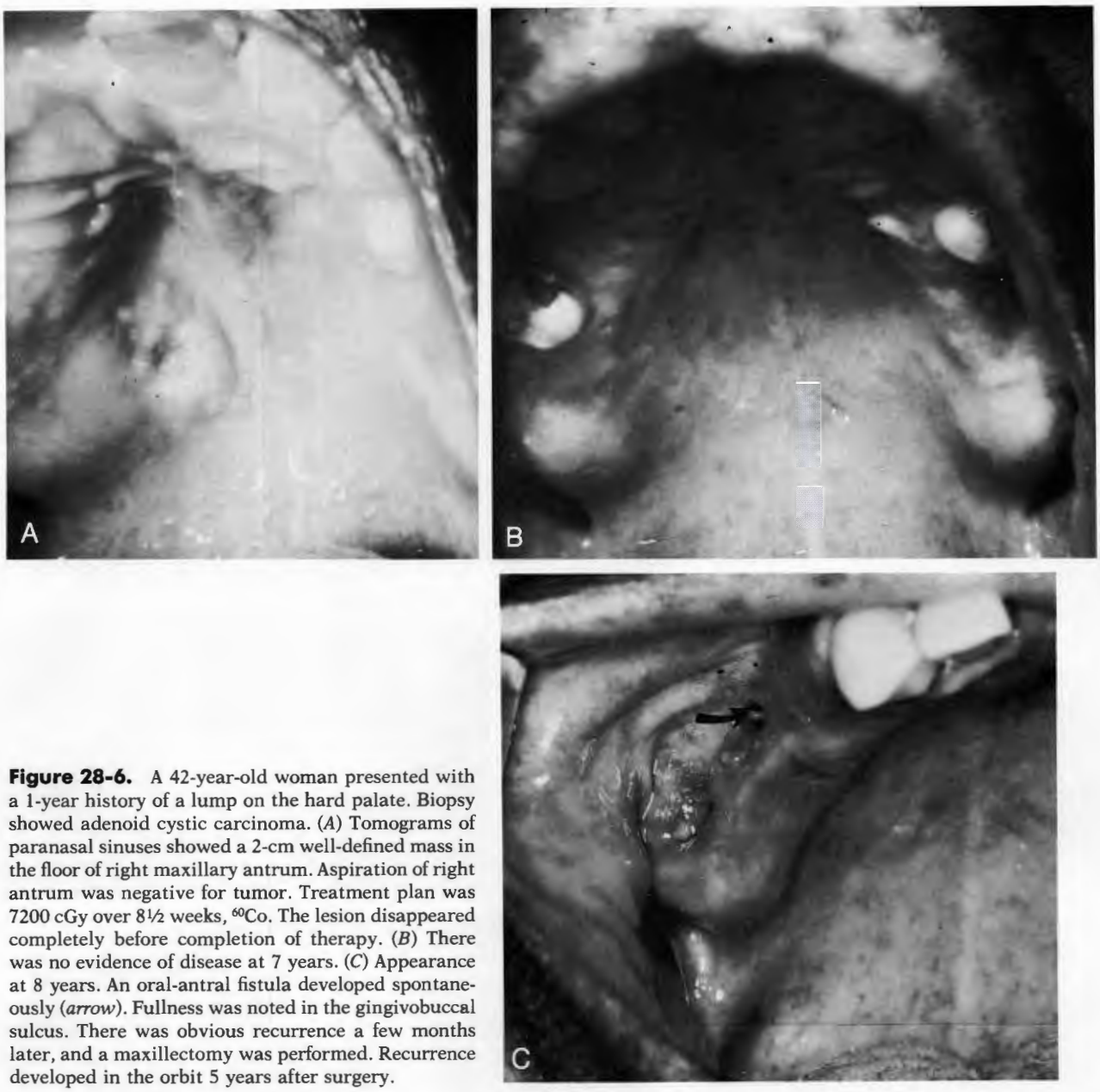

Figure 28-6. A 42-year-old woman presented with a 1-year history of a lump on the hard palate. Biopsy showed adenoid cystic carcinoma. (*A*) Tomograms of paranasal sinuses showed a 2-cm well-defined mass in the floor of right maxillary antrum. Aspiration of right antrum was negative for tumor. Treatment plan was 7200 cGy over 8½ weeks, ^{60}Co. The lesion disappeared completely before completion of therapy. (*B*) There was no evidence of disease at 7 years. (*C*) Appearance at 8 years. An oral-antral fistula developed spontaneously (*arrow*). Fullness was noted in the gingivobuccal sulcus. There was obvious recurrence a few months later, and a maxillectomy was performed. Recurrence developed in the orbit 5 years after surgery.

Management of Recurrence

Minor salivary gland tumors have a reputation for late recurrence, but *70% of recurrences appear within 2 years.* Most of the late failures occur in the adenoid cystic carcinomas. Local recurrences in the tumor bed are usually easy to diagnose, but recurrences that develop from perineural spread are often difficult to diagnose. The symptoms and signs often precede the changes in CT or MRI scans by many months. Neurologic symptoms or signs should be considered evidence of recurrence until proved otherwise.

Patients with recurrent lesions are often salvaged by subsequent therapy. Most reported series have a high proportion of previously treated patients, and yet a considerable number of patients with recurrences have a prolonged, useful life with further treatment. There are some patients (usually with adenoid cystic carcinoma) who have recurrent disease for whom there is no reasonable treatment available, and they are merely observed. Some of these observed patients lead a reasonably good life for several months or years with minimal symptoms and should not be harassed by inappropriate therapy.

RESULTS OF TREATMENT

Spiro and coworkers[13] reported the Memorial Sloan-Kettering results for 434 malignant minor salivary gland tumors, of which 90% were treated surgically. The cause-specific 5-, 10-, and 15-year cure rates were 44%, 32%, and 21%, respectively; 51% died of the original cancer. Patients with adenoid cystic carcinoma had the poorest prognosis, with about 20% surviving without recurrence.

Figure 28-7. A 14-year-old boy presented with epistaxis. There was 2 × 2-cm bulge on the left side of the nose and a mass enlarging the left inferior turbinate that did not decongest. Biopsy revealed adenoid cystic carcinoma. Tomograms showed no sinus or orbital involvement. (*A*) Mass of left lateral nose. Treatment plan was to use anterior and left lateral portals, ^{60}Co, 6500-Cgy minimum tumor dose (7000 cGy maximum) over 9 weeks (split course). There was approximately 50% regression at completion of radiation therapy. (*B*) A persistent, well-encapsulated mass was resected 2 months later. Pathology showed adenoid cystic carcinoma. The patient was free of disease at 16 years.

Those with adenocarcinoma had an intermediate outlook, about 35% surviving without recurrence. Mucoepidermoid carcinomas had the best control rate, with about 70% long-term cures. Local control differed considerably by site (Table 28-2), but this difference is partly explained by the higher incidence of advanced adenoid cystic carcinoma in the sinuses. Local control was also better for small lesions and those without bone or lymph node involvement. Previous treatment had little effect on cure rate.

Bardwil and coworkers[1] reported a similar series (87 cases) from M.D. Anderson Hospital with shorter follow-up (3 to 20 years) in which surgery was the sole treatment in 82% of cases (Table 28-3). Local control was reported to be 75%, but 47% of the patients died of their original cancer, a percentage similar to that of the Memorial Sloan-Kettering series.[7]

Schell and associates (Schell S, Barkley HT Jr, Chiminazzo H Jr. Malignant tumors of minor salivary glands, unpublished study, 1983) analyzed the M.D. Anderson Hospital results from 1970 to 1978 for a group of 118 malignant minor salivary gland tumors of which only 10% were treated by operation alone, 58% by surgery plus radiation therapy, and 32% by radiation therapy alone (see Table 28-3). The group treated by radiation therapy alone included 15 early and 23 advanced lesions. Follow-up was 2 to 10 years. The initial local control rate for the entire group was 79%, and 11 patients were salvaged by subsequent operation for an ultimate control of 88%. The risk of local recurrence by treatment category and histology is shown in Table 28-4. The low incidence of recurrence with radiation therapy alone for adenoid cystic carcinoma indicates that this histology responds initially to radiation, which corresponds with our own observations. There are too few cases in the other categories to reach any conclusions except that surgery plus radiation therapy seems to provide better initial control than surgery alone for high-grade lesions; however, the eventual survival may be only slightly enhanced. Byers and coworkers[2] reported 14 patients with malignant minor salivary gland tumors of the lip. This is a rare presentation, representing 1% of all malignant minor salivary gland tumors, and 1% of all lip cancers seen at the M.D. Anderson Hospital. Ten occurred on the lower lip, which is contrary to most reports. The disease-free survival rate was approximately 20%. These researchers recommended that all but the smallest lesions be treated with a combination of surgery and radiation therapy. There was a substantial risk for regional node and perineural invasion.

Weber and associates[17] reviewed 31 malignant lesions of the buccal mucosa and 15 of the lip managed by surgery or irradiation or both. The recurrence rate was 21% for the lip and 6% for the buccal mucosa.

Ellis and associates[4] reported the results for 52 malignant minor salivary gland tumors managed either by radiation therapy (26 patients) as the initial treatment or

TABLE 28-2. Results of Surgical Treatment of Minor Salivary Gland Tumors (267 Patients*)

Site	Patients	Local Control (%)
Oral cavity/oropharynx	198	68
Sinus/nasal/nasopharynx	58	28
Larynx	11	55

* 60%, no prior treatment; 14%, clinically positive nodes on admission; 90% treated surgically; follow-up 5 years.

Note: Memorial Sloan-Kettering Hospital data; patients treated 1939 to 1963.

(Data from Spiro RH, Koss LG, Hajdu SI, Strong EW. Tumors of minor salivary origin: a clinicopathologic study of 492 cases. Cancer 1973;31:117–129)

TABLE 28-3. Results of Treatment of Malignant Minor Salivary Gland Tumors (M.D. Anderson Hospital)

Study	Patients	Treatment		No Prior Treatment (%)	Follow-Up (y)	Local Control (%)	Distant Metastases (%)	DOD or LWD (%)
		Method	Patients					
Bardwil and coworkers[1] (1945–1962)	87	S	71	56	3–20	75	30	47
		S plus RT	10					
		RT	6					
Schell and coworkers* (1970–1978)	118	S	11	42	2–10	79†	25	36
		S plus RT	69					
		RT	38					

* Data from unpublished study of M.D. Anderson data by Schell S, Barkley HT Jr, Chiminazzo H Jr. Treatment of malignant minor salivary gland tumors. 1983.
† Eleven patients had repeated operations, for an ultimate control rate of 88%.
DOD = dead of disease; LWD = living with disease; S = surgery; RT = radiation therapy.
(Million RR, Cassisi NJ, Clark JR. Cancer of the head and neck. In: DeVita VT Jr, Hellman S, Rosenberg SA, eds. Cancer: principles and practice of oncology, ed 3. Philadelphia, JB Lippincott, 1989:582)

TABLE 28-4. Malignant Minor Salivary Gland Tumors: Primary Recurrence Related to Treatment Modality

Histology	Patients With Recurrence After Initial Treatment/Total Patients Treated			
	Surgery Only	Surgery Plus Radiation Therapy	Radiation Therapy Alone	Total
High grade				
Adenoid cystic	3/4	9/40	0/23	12/67
Mucoepidermoid	0/1	0/6	4/7	4/14
Adenocarcinoma	3/4	3/14	1/4	7/22
Malignant mixed	0/0	0/1	0/0	0/1
Low grade				
Mucoepidermoid	1/2	0/7	1/4	2/13
Acinic cell	0/0	0/1	0/0	0/1
TOTAL	7/11*	12/69†	6/38	25/118

* Five patients salvaged by repeated surgical resection.
† Six patients salvaged by surgery.
Note: M.D. Anderson Hospital data from unpublished study by Schell S, Barkley RT Jr, Chiminazzo H Jr. Treatment of malignant minor salivary gland tumors. 1983.

TABLE 28-5. Local Control at Primary Site for Early-Stage Tumors

Histology	Patients	Excluded*	Radiation Therapy Alone	Radiation Therapy Plus Surgery
Adenoid cystic	12	1	3/4	5/7
Adenocarcinoma	3	0	No data	3/3
Mucoepidermoid	2	0	2/2	No data
Malignant mixed	2	0	1/1	1/1
TOTAL	19	1	6/7 (86%)	9/11 (82%)

* Died of distant metastasis only or intercurrent disease less than 2 years after treatment (primary tumor controlled).
(Ellis ER, Million RR, Mendenhall WM, Parsons JT, Cossisi NJ. The use of radiation therapy in the management of minor salivary gland tumors. Int J Radiat Oncol Biol Phys 1988;15:615)

TABLE 28-6. Local Control at Primary Site for Advanced-Stage Tumors

Histology	Patients	Excluded*	Radiation Therapy Alone	Radiation Therapy Plus Surgery
Adenoid cystic	14	2	0/7	3/5
Adenocarcinoma	10	2	1/4	3/4
Mucoepidermoid	7	3	1/1	3/3
Malignant mixed	2	0	0/1	1/1
TOTAL	33	7	2/13† (15%)	10/13† (77%)

* Died of distant metastasis only or intercurrent disease less than 2 years after treatment (primary tumor controlled).
† $P = .003$.
(Ellis ER, Million RR, Mendenhall WM, Parsons JT, Cassisi NJ. The use of radiation therapy in the management of minor salivary gland tumors. Int J Radiat Oncol Biol Phys 1988;15:615)

surgery and radiation therapy (26 patients). Minimum follow-up was 2 years, and 80% had a minimum 5-year follow-up. Forty percent had tumors of the nasal cavity or paranasal sinuses and about half had cancers of the oral cavity or oropharynx. Advanced lesions were considered to be AJCC stage III or IV, lesions greater than 5 cm or those with extensive bone or nerve involvement. Twelve percent had clinically positive nodes. Local control is given by histology and by initial treatment in Tables 28-5 and 28-6. Actuarial local control curves are shown in Figure 28-8, cause-specific survival by histology is shown in Figure 28-9, and cause-specific survival by anatomic site is shown in Figure 28-10.

Three of four patients with early-stage adenoid cystic carcinomas survived with no evidence of disease for 9, 9, and 11 years after receiving radiotherapy alone.[4] Although long-term local control was never achieved in nine patients with advanced-stage adenoid cystic carcinoma treated with radiation therapy alone, their disease-free survival times were often prolonged. The average time to local recurrence was 67 months; in two of these patients, the recurrences were 9 and 13 years after radiotherapy, and one is alive with disease at 20 years. The time to death was also prolonged with four patients living 4, 4, 6, and 10 years posttreatment.[4]

Vrielinck and associates[16] reviewed 37 patients with adenoid cystic carcinoma of the major and minor salivary glands managed by combined surgery and radiation therapy. Perineural invasion was diagnosed in 52%. The results are shown according to surgical margin and perineural invasion in Table 28-7. Nerve invasion increased in incidence with T stage: 45% for T1 and T2 lesions and 77% for T3 and T4 lesions. Local-regional recurrence, distant metastasis, and 5-year survival correlated with perineural invasion (Table 28-8).

Cohen and associates[3] reviewed 18 cases of major and minor salivary gland tumors of the larynx (14 were supraglottic and 4 were subglottic). Six patients presented with lymph node metastases, and three additional patients developed lymph node metastases after initial treatment. Twelve were stage III and IV. One of two T1 lesions was cured by radiation therapy; the lesion that recurred was cured by total laryngectomy. The remaining 16 were managed by surgery; radiotherapy was added in 5. Only three patients remained free of disease at the time of the report.

Bardwil and coworkers[1] reported 13 patients with benign mixed tumors, all of whom were cured, 12 by operation and 1 by radiation therapy alone. Five patients with benign mixed tumors were treated at the University of Florida, and all five had control of disease (Table 28-9).

Rafla-Demetrious[10] reported the Royal Marsden experience of 44 cases of benign mixed tumor (Table 28-10). Eleven patients were treated by radiation therapy alone, and none of the tumors regrew, although not all had complete regression. Several photographs in Rafla's

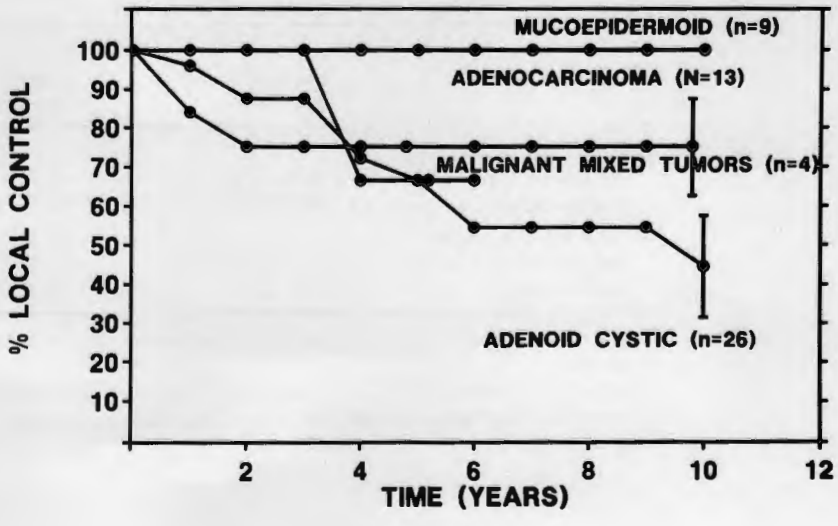

Figure 28-8. Actuarial control of disease at the primary site by histology. Bars depict ±1 standard error at 10 years. (Ellis ER, Million RR, Mendenhall WM, Parsons JT, Cassisi NJ. The use of radiation therapy in the management of minor salivary gland tumors. Int J Radiat Oncol Biol Phys 1988;15:614)

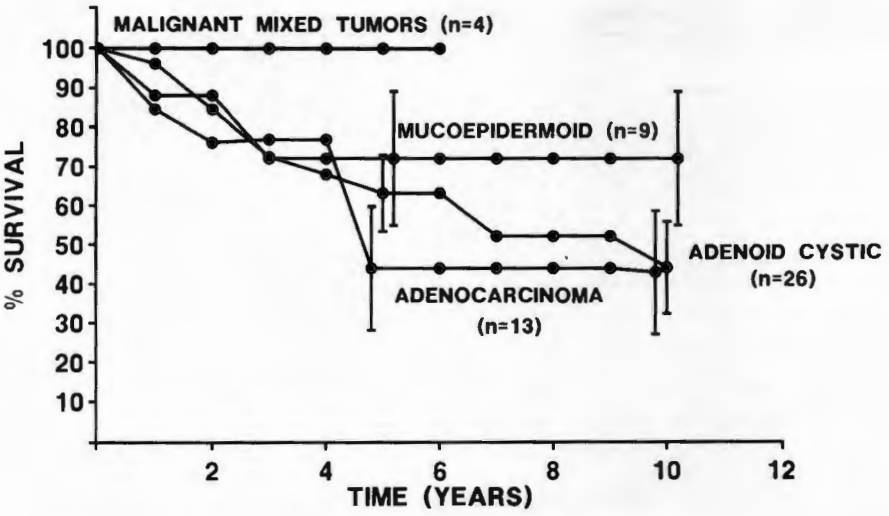

Figure 28-9. Actuarial cause-specific survival by histology. Bars depict ±1 standard error at 5 and 10 years. (Ellis ER, Million RR, Mendenhall WM, Parsons JT, Cassisi NJ. The use of radiation therapy in the management of minor salivary gland tumors. Int J Radiat Oncol Biol Phys 1988;15:616)

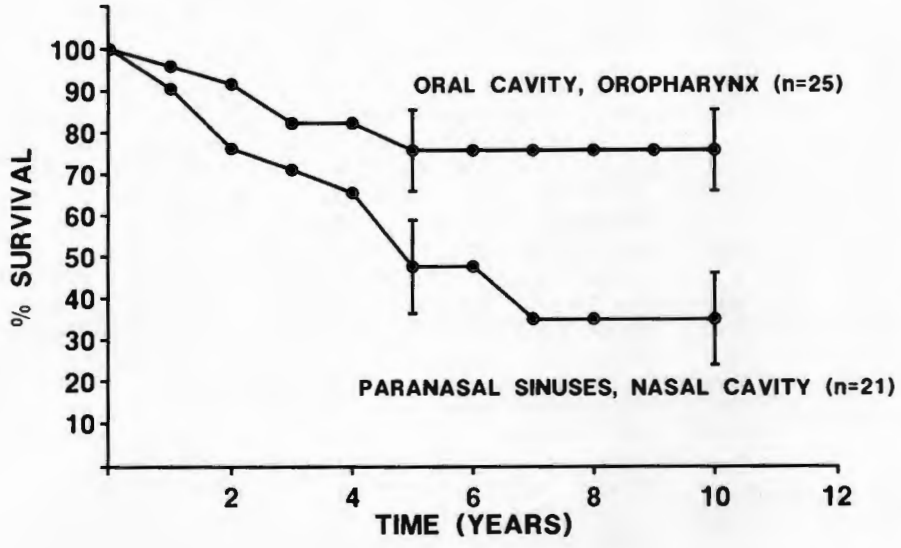

Figure 28-10. Actuarial cause-specific survival by the site of primary disease ($P = .06$). Bars depict ±1 standard error at 5 and 10 years. (Ellis ER, Million RR, Mendenhall WM, Parsons JT, Cassisi NJ. The use of radiation therapy in the management of minor salivary gland tumors. Int J Radiat Oncol Biol Phys 1988;15:616)

TABLE 28-7. Adenoid Cystic Carcinoma: Recurrence at the Primary Site or Distant Metastasis in Relation to the Status of the Surgical Margin and Perineural Invasion

	Local–Regianal Recurrence	Distant Metastasis	5- and 10-Year Actuarial Survival Rate
Perineural invasion			37%
Negative margin	5/11 (45%)	4/10 (40%)*	
Positive margin	6/8 (75%)	5/8 (62%)	
No perineural invasion			94%
Negative margin	4/15 (27%)	0/14 (0%)*	
Positive margin	0/3 (0%)	0/3 (0%)	

* One patient in this group already had lung metastasis at initial presentation and is therefore not included in the table.

(Modified from Vrielinck LJG, Ostyn F, Van Damme B, Van den Bogaert W, Fossion E. The significance of perineural spread in adenoid cystic carcinoma of the major and minor salivary glands. Int J Oral Maxillofac Surg 1988;17:192)

TABLE 28-8. Adenoid Cystic Carcinoma: Incidence of Local–Regional Recurrence and Distant Metastasis According to Perineural Invasion

Nerve Invasion	Local–Regional Recurrence	Distant Metastasis	5- and 10-Year Actuarial Survival Rate
Positive	11/19 (58%)	9/18 (50%)*	37%
Negative	4/18 (22%)	0/17 (0%)*	94%

* One patient in this group already had lung metastasis at initial presentation and is therefore not included in the table.
(Modified from Vrielinck LJK, Ostyn F, Van Damme B, Van den Bogaert W, Fossion E. The significance of perineural spread in adenoid cystic carcinoma of the major and minor salivary glands. Int J Oral Maxillofac Surg 1988;17:192)

TABLE 28-9. Benign Minor Salivary Gland Tumors

	Locally Controlled/Treated		
Method of Treatment	Local Control	Salvage	Ultimate Control
Surgery	2/3	1/1	3/3
Surgery plus radiation therapy	2/2	0	2/2

Note: University of Florida data; patients treated January 1960 to April 1978; analysis April 1980 by JR Russell, MD.

TABLE 28-10. Incidence of Recurrence of Pleomorphic Adenoma of Minor Salivary Glands in the Royal Marsden Series: Distribution According to the Method of Treatment

Method of Treatment	Patients	Recurrence	Patients and Length of Follow-Up
Radiation alone	11	0	5 for 5+ y
Preoperative irradiation and surgery	14	2	9 for 5+ y
Surgery and postoperative irradiation	18	0	14 for 5+ y 9 for 10+ y
Surgery alone	1	0	1 for 5 y
TOTAL	44	2	29 for 5+ y

(Rafla-Demetrious SF. Mucous and salivary gland tumours. Springfield, Charles C Thomas, 1970:118)

book demonstrate the response to radiation therapy. Local recurrence of benign mixed tumor may appear after many years, and an occasional patient may eventually die of uncontrolled disease.

FOLLOW-UP POLICY

The majority of local recurrences appear by 2 or 3 years, but the benign mixed tumors and adenoid cystic carcinomas may show a recurrence many years after initial treatment. Early recognition of recurrence may be important because in some patients salvage is achieved by further treatment.

COMPLICATIONS OF TREATMENT

The surgical and radiation complications are similar to those already outlined for each anatomic site. Unilateral blindness was the most common severe radiation complication, occurring in nine patients at the University of Florida. However, seven of these patients had unresectable disease with close proximity to or invasion of the orbit. In these patients, unilateral blindness would have resulted anyway either from uncontrolled tumor growth or from an attempted surgical procedure. Thirteen eye complications that did not lead to blindness occurred in nine patients (Table 28-11). Owing to the large number of different sites of disease, a wide variety of other mild and

TABLE 28-11. Eye Complications Not Leading to Blindness (40 Patients)*

Complication	Patients
Retinopathy	2
Optic neuropathy	1
Cataract	2
Dry eye syndrome	4
Dacryocystitis	1
Injury to nasal lacrimal drainage system	2
Lid edema/fibrosis	1
TOTAL	13

* Excludes 11 patients with local recurrence or death less than 2 years after treatment ond 1 patient in whom follow-up information was incomplete.

(Ellis ER, Million RR, Mendenhall WM, Parsons JT, Cassisi NJ. The use of radiation therapy in the management of minor salivary gland tumors. Int J Radiat Oncol Biol Phys 1988;15:616)

moderate complications occurred. No complications occurred in 10 of the 40 evaluated patients.[4]

Because a high percentage of minor salivary gland tumors arise in or invade the paranasal sinuses or nasal cavity, severe irradiation complications can occur. These complications must be weighed against the morbidities of a major operation or the potential local effects of uncontrolled tumors. CT and MRI have allowed better definition of the extent of tumor growth, thereby limiting the treatment volume with hopes of decreasing the incidence of severe complications. An improved knowledge of the safe doses to the eye has diminished the eye complications, and the combination of base of skull surgery with lesser doses of radiation therapy should also reduce the eye complications.

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29

TEMPORAL BONE

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Primary carcinomas of the external auditory canal and middle ear are uncommon. They are usually associated with a long-standing history of chronic infection, and with the availability of antibiotics, the problem of chronic infection has been significantly reduced. Metastatic lesions and secondary invasion of the temporal bone by tumors arising from contiguous areas are more common. Temporal bone tumors are often misdiagnosed until advanced, at which time the success of therapy is understandably poor. This section deals mainly with the carcinomas (see Chap. 30).

ANATOMY

The temporal bone is a complex structure housing the organs of hearing and balance. It is traversed by the internal carotid artery, internal jugular vein, and the facial, vestibulocochlear, glossopharyngeal, vagus, and spinal accessory nerves and some of their branches.

The cartilaginous portion of the external ear canal is covered by skin with numerous hair follicles and sebaceous and ceruminous glands. The skin of the bony portion of the canal is firmly adherent to the underlying periosteum. The canal, which is 2 to 4 cm in length, is formed by bone over the medial two thirds and fibrocartilage over the outer one third. The cartilage is incomplete, particularly superiorly and posteriorly; the intervals are filled with fibrous tissue. Immediately anterior to the external auditory canal are the temporomandibular joint and the parotid gland. Behind the canal is the mastoid bone, and inferiorly the canal is in relation to the tail of the parotid and the facial nerve. Lymphatic drainage is to the preauricular, jugular chain, and mastoid lymph nodes. The tympanic membrane probably has significant capillary lymphatics on the external surface only.

The middle ear is subdivided into the tympanic cavity, mastoid, and eustachian tube. The tympanic cavity and mastoid antrum and air cells are lined by columnar epithelium, both ciliated and nonciliated. The epithelium is continuous along the eustachian (auditory) tube to the nasopharynx. The epithelium lining the cartilaginous portion of the eustachian tube is thick and vascular and contains numerous mucous glands; the epithelium is ciliated columnar.

The tympanic cavity and mastoid probably do not have significant capillary lymphatics[17] nor does the internal ear (labyrinth). Capillary lymphatics are described for the mucous membrane of the cartilaginous portion of the eustachian tube; the drainage is to the jugular chain and retropharyngeal lymph nodes. A potential pathway from the eustachian tube to the preauricular nodes was described by Arnould.[1]

The internal ear or labyrinth is lined by epithelium and presumably could be the site of a primary carcinoma, although no record of such has been found.

PATHOLOGY

A rare benign neoplasm is squamous cell papilloma, usually occurring in the external auditory canal and rarely in the middle ear.[16] These tumors are more frequent in people in southern China and are said to be sensitive to irradiation.

Chemodectomas are the most common neoplasm seen in the temporal bone. They are best considered as low-grade malignancy in the sense that they are locally aggressive tumors that rarely disseminate to regional lymph nodes or distant sites (see Chap. 30).

Carcinomas of the external auditory canal are essentially squamous cell or basal cell skin carcinomas; malignant melanoma may also arise in the canal. Ceruminous gland adenocarcinoma is a rare tumor developing from the modified sweat glands of the external auditory canal.[21] Tumors arising from the tympanic cavity, mastoid, or eustachian tube include squamous cell carci-

noma and benign and malignant salivary gland tumors, particularly along the medial two thirds of the eustachian tube and the middle ear. Twenty-six cases of middle ear adenomas and adenocarcinomas have been reported.[14]

Hemangiomas and tumors of neural origin may occur along the course of the facial nerve.

Embryonal cell rhabdomyosarcoma is a rare sarcoma of the middle ear occurring in children. The histiocytoses frequently involve the temporal bone. Ewing's sarcoma and osteosarcoma have been reported but are rare (see Chaps. 32 and 33). Metastases occur to the temporal bone and must be distinguished from lesions originating in the temporal bone. The breast is a common site for a primary lesion.[7]

PATTERNS OF SPREAD

External Auditory Canal

Basal cell carcinoma of the external auditory canal tends to begin in the entrance to the canal. As the lesion progresses, it quickly attaches to the perichondrium and eventually invades and destroys cartilage and extends to the concha, the tympanic membrane, and finally the middle ear and mastoid.

A squamous cell carcinoma of the external auditory canal may occur anywhere along the canal. It may appear as a red, polypoid mass, usually associated with chronic infection. Because growth is contained by the bony/cartilaginous walls and the tympanic membrane, the neoplasm tends to fill up the canal and attach to underlying perichondrium or periosteum. Eventually, the tumor invades cartilage or bone, or grows through the tympanic membrane to reach the middle ear, mastoid, and facial nerve.

Jesse and coworkers[8] reported a 21% incidence of lymph node metastases on admission for squamous cell carcinoma.

Middle Ear: Tympanic Cavity, Mastoid, and Eustachian Tube

Because the areas of the middle ear are not readily available for visual examination, the growth pattern of early lesions remains speculative. When first diagnosed, most lesions have already destroyed bone and invaded cranial nerves and the sensory organs of hearing and balance. The neoplasm may proceed along any of several routes. The temporal bone is literally riddled with numerous channels carrying nerves, muscles, the eustachian tube, and blood vessels; these tunnels allow spread without destroying bone.

Posterior growth through the mastoid brings tumor to the sigmoid sinus and contents of the posterior cranial fossa.

Superior extension occurs through the thin roof of the tympanic cavity (tegmen tympani) to the middle cranial fossa.

Erosion through the thin floor of the hypotympanic recess brings the tumor into relationship with the tail of the parotid, facial nerve, jugular vein, internal carotid artery, and soft tissues of the upper neck.

The tumor may extend medially and anteriorly along the eustachian tube to the nasopharynx; this spread pattern is often accompanied by destruction of the petrous apex and possible extension into the carotid canal. Anterior growth eventually invades into the temporomandibular joint, parotid gland, and parapharyngeal space.

Access to the cranial cavity is through direct bony penetration or along the facial, vestibulocochlear, lesser superficial petrosal, and auriculotemporal nerves.

Lymphatic spread is unusual, because significant capillary lymphatics occur only in the medial two thirds of the eustachian tube. Boland and Paterson[3] reported lymph node metastases on admission in 10 (12%) of 86 patients.

CLINICAL PICTURE

External Auditory Canal

The initial symptom is similar to that of any skin cancer—a painless lesion in the canal. As the lesion enlarges, the patient may notice minor bleeding, pain, itching, and intermittent serous drainage. Both the patient and the physician assume that the diagnosis is external otitis, and local treatment is prescribed over a period of several months. A loss of hearing occurs when the canal is occluded or when the tumor involves the tympanic membrane or middle ear. Pain may be severe in advanced cases.

Early lesions of the external canal appear as a nodule, possibly with crusts and dried blood from scratching. As the lesions enlarge, they tend to grow under the skin and produce narrowing of the canal with the appearance of a polypoid mass filling the canal. Examination of the tympanic membrane is aided by an operating microscope and suction because a large amount of debris is frequently present. A preauricular mass or fullness may be found due to parotid invasion, and trismus may result with invasion of the temporomandibular joint. The tumor may be seen eroding into the posterior auricular sulcus. The concha is often involved.

Middle Ear: Tympanic Cavity, Mastoid, and Eustachian Tube

Carcinomas of the middle ear are associated with chronic ear infection in the majority of patients, many of whom have had a mastoid operation. The onset of symptoms due to cancer is associated with increasing pain and discharge. The pain may be severe and is usually temporal. Facial nerve palsy is a common cause for seeking medical advice. Hearing loss is often present from the chronic otitis, but there may be further loss due to the neoplasm. Vertigo and tinnitus are infrequent. Cranial nerves II through XII may be invaded.

A rare lesion probably arises in the eustachian tube and produces syndromes that mimic nasopharyngeal cancer. The patient has pain, otitis with hearing loss, and cranial nerve deficits due to involvement of the cavernous sinus and erosion of the petrous apex and adjacent base of the skull. The nasopharynx is normal on examination, which delays diagnosis. Lederman and coworkers[9] described four such cases, and we have observed two cases at the University of Florida. Computed tomography (CT) and magnetic resonance imaging (MRI) are helpful in these rare cases.

On physical examination, a small mass may be seen on the tympanic membrane, or, more often, the deep portion of the external auditory canal is blocked by a friable, bleeding tumor. There may be diffuse edema and erythema of the external auditory canal or of the skin around the concha. Tugging on the pinna may cause pain. Anterior growth may be associated with trismus. A submucosal mass may be seen in the nasopharynx. Cranial nerves should be evaluated.

METHODS OF DIAGNOSIS AND STAGING

The differential diagnosis of external auditory canal lesions includes the following:

Extension of middle ear tumor to the external auditory canal
Otitis externa
Malignant (necrotizing) external otitis (*Pseudomonas* infection occurring in diabetes mellitus)
Squamous cell papilloma
Foreign body
Furuncle
Osteoma
Epidermoid (congenital) cholesteatoma
Eosinophilic granuloma

The differential diagnosis of carcinomas of the middle ear, mastoid, or eustachian tube lesion includes the following:

Chronic otitis media
Cholesterol granuloma[13]
Cholesteatoma
Mastoiditis
Glomus tumors
Metastatic cancer
Carcinoma of the nasopharynx
Acoustic schwannoma or neurilemmoma
Facial nerve schwannoma or hemangioma
Fibrous dysplasia
Meningioma

If a mass is readily accessible in the external auditory canal or neck, biopsy may be performed immediately; if not, CT and possibly MRI should precede exploration and biopsy (see Chap. 30). There is no staging system for these rare tumors.

Pretreatment work-up should include audiometric evaluation.

Diagnostic Imaging

CT is normally the first study used because the assessment of bone detail is critical to treatment planning. MRI is a frequently used adjunct in advanced lesions. Both CT and MRI are usually adequate for evaluating the status of the sigmoid and transverse sinuses and carotid artery.

Examination Technique

CT must be done with sections no thicker than 1.5 mm and with the highest possible spatial resolution (ie, small field of view). These must be processed with bone as well as soft tissue algorithms, and direct (rather than reformatted) coronal sections are almost always required in addition to the standard axial sections. MRI should be focused to the precise area of interest and done with high-resolution, thin-section techniques.

Imaging of the Normal Anatomy

The normal CT anatomy of the temporal bone is presented in Figures 29-1 and 29-2.[12]

Indications for Imaging

DIFFERENTIAL DIAGNOSIS. Lesions of the external canal are normally accessible for biopsy. A submucosal or subcutaneous mass should be studied with CT, and MRI in selected cases, before biopsy. Questionable lesions (eg, noncholesteatomatous) medial to the tympanic membrane are best studied before biopsy; this can prevent unnecessary exploration or hemorrhagic complications (eg, in the case of a middle ear extension of a glomus jugulare tumor; see Figs. 30-3 through 30-5) or other rare complications (eg, the inadvertent biopsy of a carotid artery or meningoencephalocele).

EXTENT OF THE TUMOR. CT is used to detect bone erosion at any site (Figs. 29-3 and 29-4). More advanced lesions often spread through bone far from the site of origin. Critical regions of interest for assessing medial spread include the bony and cartilaginous portions of the eustachian tube, the carotid canal, and the carotid artery. A particularly insidious pattern of medial and inferior spread is through the petrotympanic fissure or along the soft tissues posterior and medial to the temporomandibular joint and into the temporomandibular joint. A combination of multiplanar CT and MRI is used to evaluate these spread patterns.

PERINEURAL SPREAD. The predominant nerve involved is cranial nerve VII, and this may lead to involvement of the greater superficial petrosal nerve. Spread into the inner ear and along cranial nerve VIII may occur in very advanced lesions. The auriculotemporal nerve may be involved in lesions that spread to the upper parotid gland and perimandibular region.

EVALUATION OF THE CAROTID ARTERY AND DURAL VENOUS SINUSES. The proximity of tumor to the structures or their invasion by tumor is best determined by a combination of CT and MRI. MRI angiography, static MRI images, and contrast-enhanced CT can determine the dominance and patency of major dural sinuses.

Carotid arteriography with test balloon occlusion may be necessary if carotid sacrifice is anticipated. The artery can be preoperatively occluded with endovascular techniques; this is discussed more completely in Chapter 4.

TREATMENT

Selection of Treatment Modality

Radiation therapy and surgery, either alone or combined, are the only curative options. The number of cases managed even in a large cancer hospital is so small that it is impossible to gauge the relative effectiveness of excision and radiation therapy. Therefore, the selection of

(*text continues on page 758*)

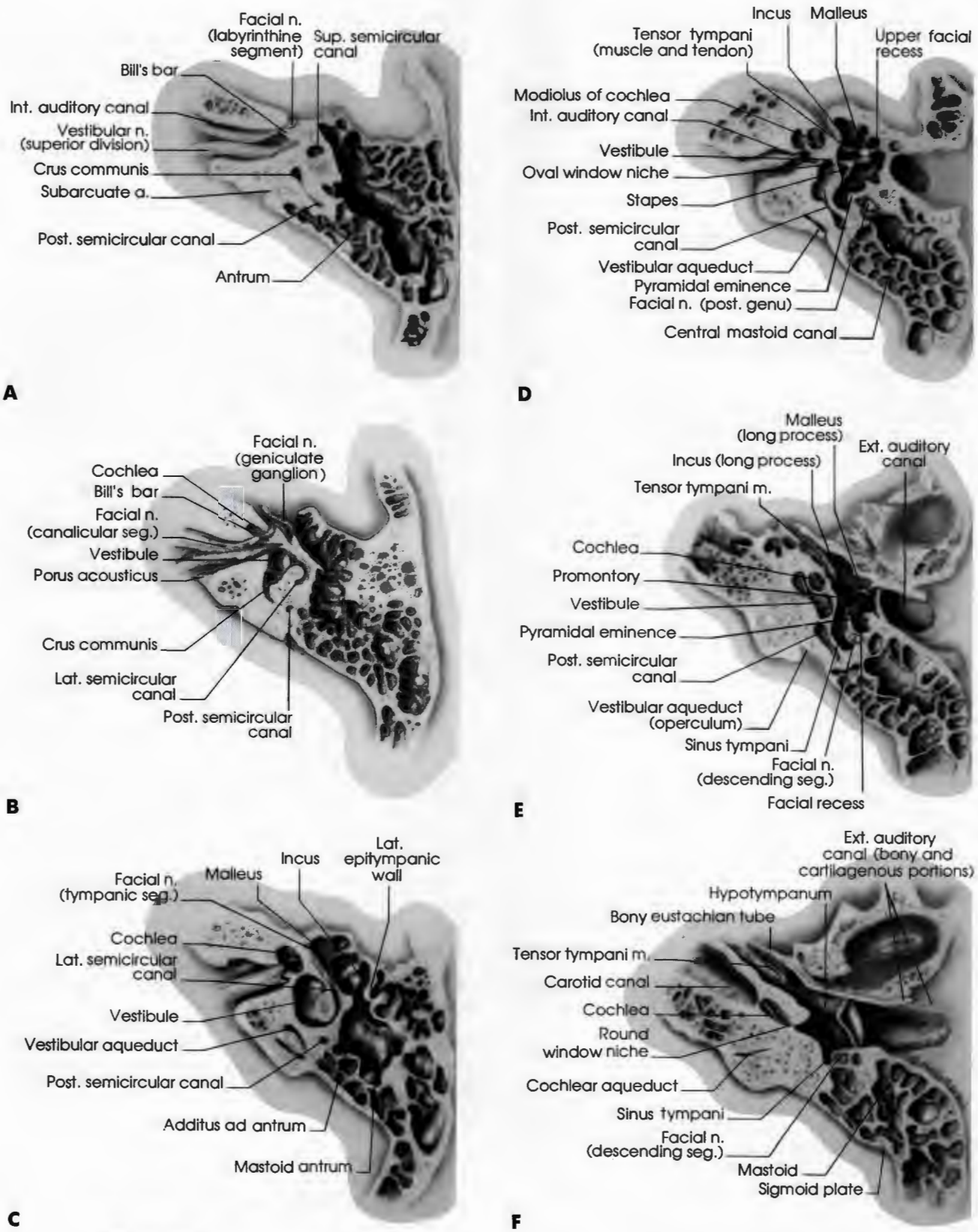


Figure 29-1. Axial diagrams and correlating CT sections of temporal bone anatomy. (Mancuso AA, Harnsberger HR, Dillon WP. Workbook for MRI and CT of the head and neck, ed 2. Baltimore, Williams & Wilkins, 1989:102–103)

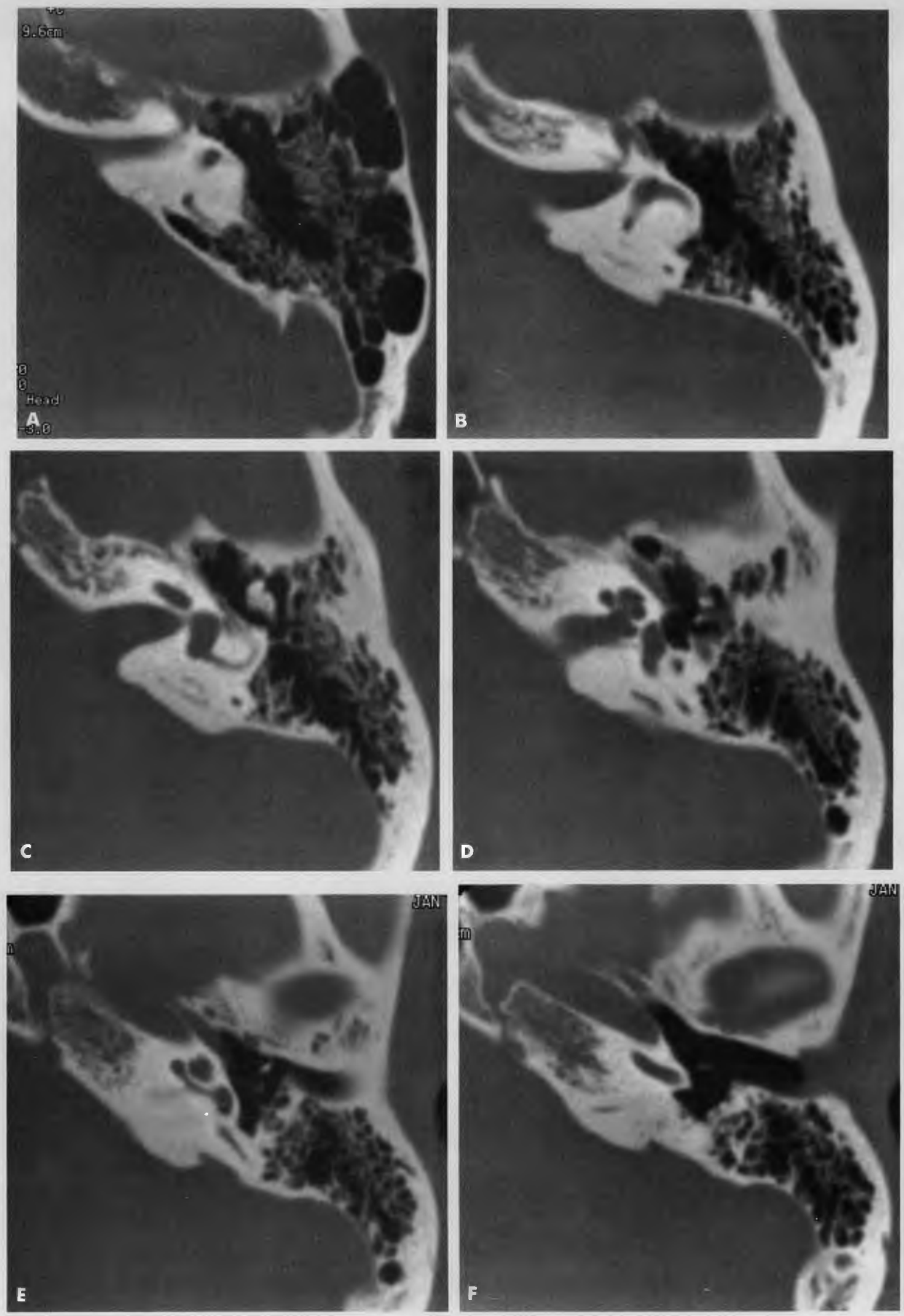


Figure 29-1. (*Continued*)

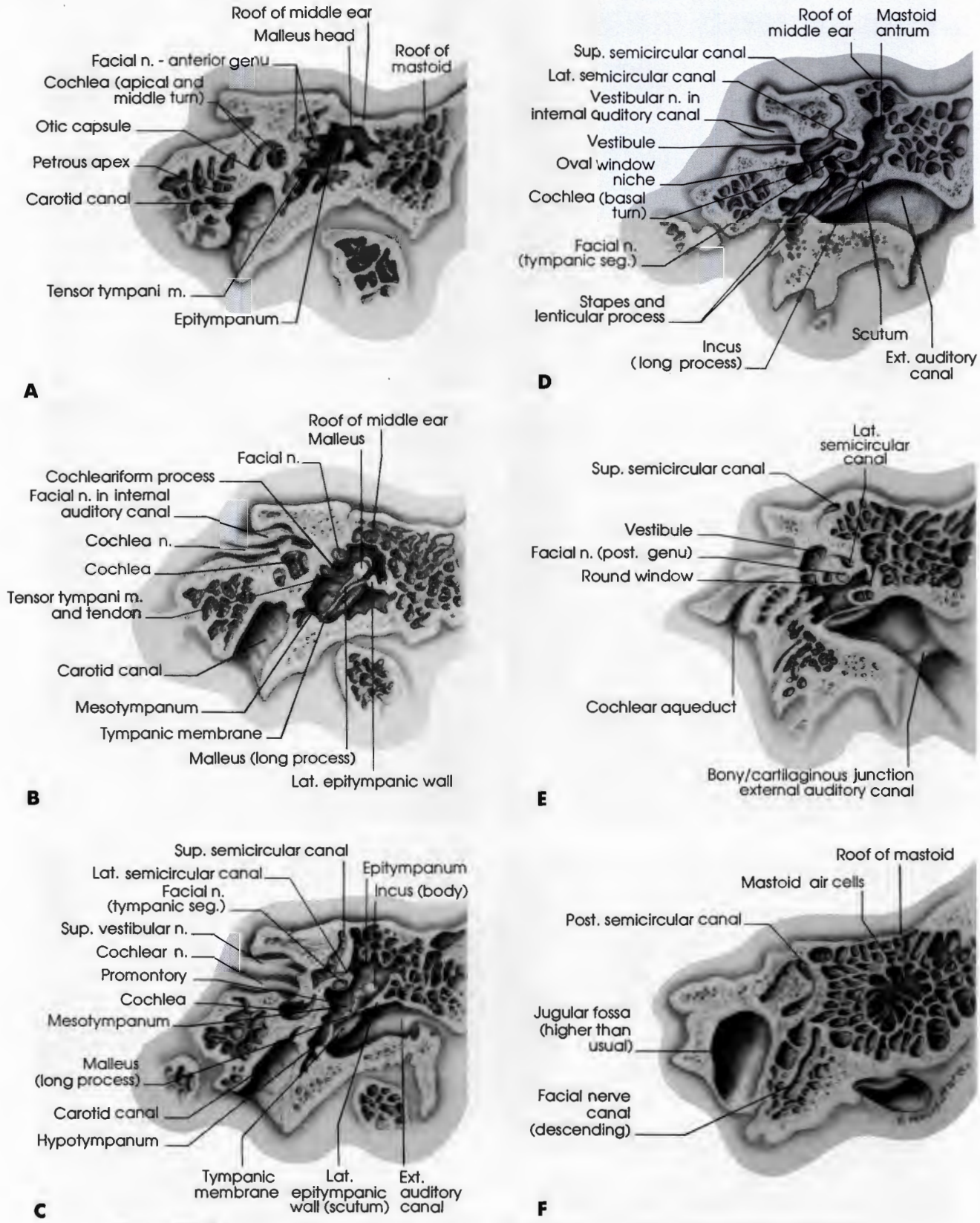
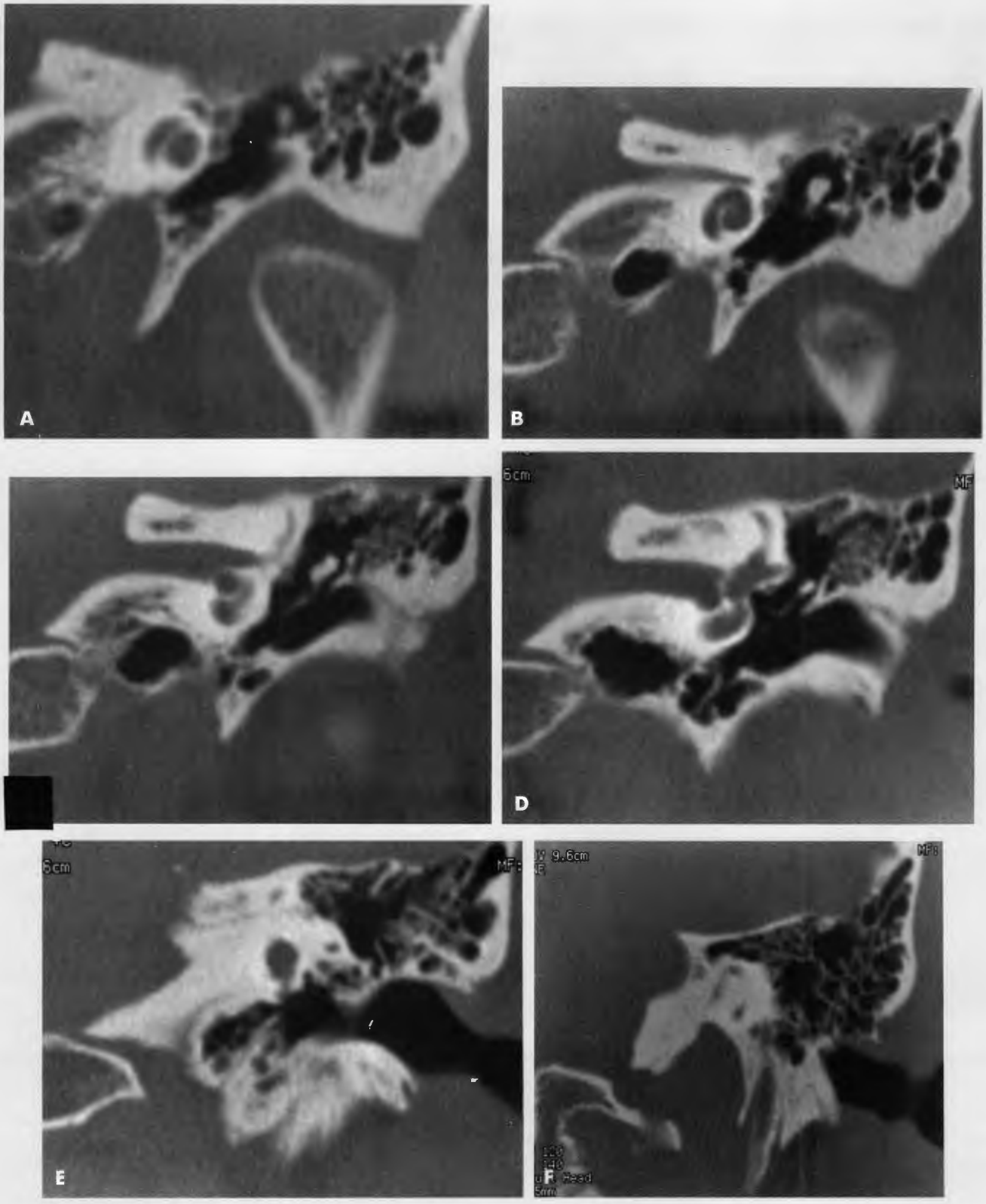


Figure 29-2. Coronal diagrams and correlating CT sections of temporal bone anatomy. (Mancuso AA, Harnsberger HR, Dillon WP. Workbook for MRI and CT of the head and neck, ed 2. Baltimore, Williams & Wilkins, 1989:104–105)



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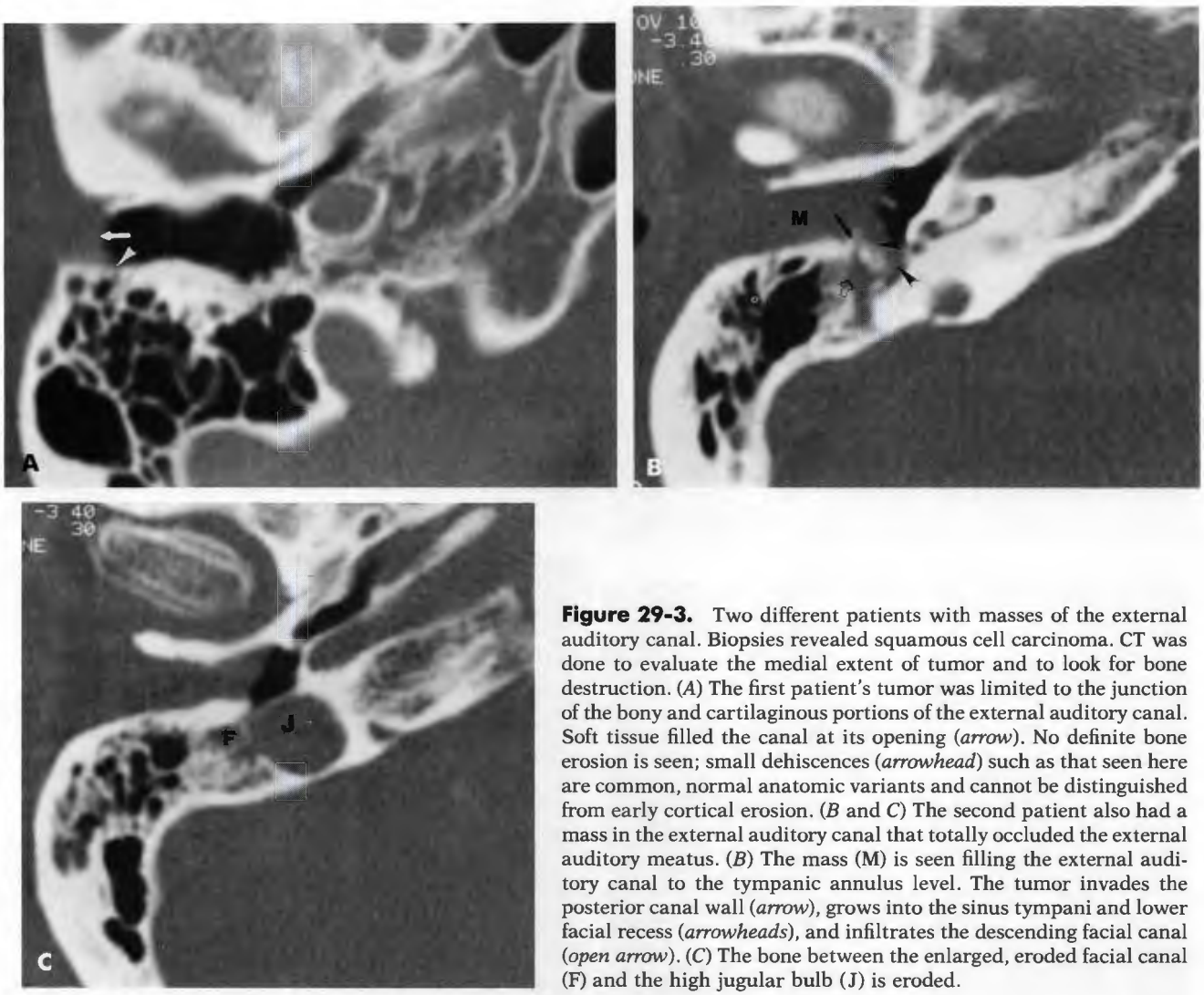

Figure 29-3. Two different patients with masses of the external auditory canal. Biopsies revealed squamous cell carcinoma. CT was done to evaluate the medial extent of tumor and to look for bone destruction. (*A*) The first patient's tumor was limited to the junction of the bony and cartilaginous portions of the external auditory canal. Soft tissue filled the canal at its opening (*arrow*). No definite bone erosion is seen; small dehiscences (*arrowhead*) such as that seen here are common, normal anatomic variants and cannot be distinguished from early cortical erosion. (*B* and *C*) The second patient also had a mass in the external auditory canal that totally occluded the external auditory meatus. (*B*) The mass (M) is seen filling the external auditory canal to the tympanic annulus level. The tumor invades the posterior canal wall (*arrow*), grows into the sinus tympani and lower facial recess (*arrowheads*), and infiltrates the descending facial canal (*open arrow*). (*C*) The bone between the enlarged, eroded facial canal (F) and the high jugular bulb (J) is eroded.

treatment modality is based more on an educated hunch than on firm data. Although the morbidity from excision of external auditory canal tumors is relatively minor, a major temporal bone resection poses the threat of immediate death and rather major morbidity, so that irradiation, even with the risk of late central nervous system damage, is often a more tempting initial modality, with operation reserved for persistence.

Surgical Treatment

The terminology describing surgical procedures used for the management of malignancies of the external auditory canal and middle ear may be confusing. The procedures are most commonly referred to as partial temporal bone resection (includes lateral temporal bone resection and sleeve resection), subtotal temporal bone resection, and temporal bone resection. Each of these approaches and its indications are described separately.

External Auditory Canal

Partial temporal bone resection describes the removal of a portion of or the entire cartilaginous and bony external auditory canal. Tumors confined to the external auditory canal and adjacent concha without involvement of the middle ear are best managed in this fashion. The most commonly performed partial temporal bone resection is termed lateral temporal bone resection and includes the removal of the entire external auditory canal, tympanic membrane, malleus, and incus. The stapes and the facial nerve are preserved (Fig. 29-5). Circumferential incisions are made around the external meatus, and a core of skin, cartilage, and bone is resected. The removal of the bony canal is accomplished by way of a mastoidectomy with facial recess approach. The middle ear space serves as the medial margin, and all structures lateral to the facial nerve are resected. The resultant defect is reconstructed with temporalis fascia or a split-thickness skin graft.

Lesions limited to the cartilaginous external auditory canal may require only the removal of the lateral bony canal or no bone at all, depending on the medial extent of the tumor. This modification of a lateral temporal bone resection is sometimes referred to as a "sleeve resection" (see Fig. 29-5).

More extensive lesions may require that the partial temporal bone resection be modified to include removal of the pinna, parotid gland, and the temporomandibular joint.

Excision of tumors confined to the cartilaginous exter-

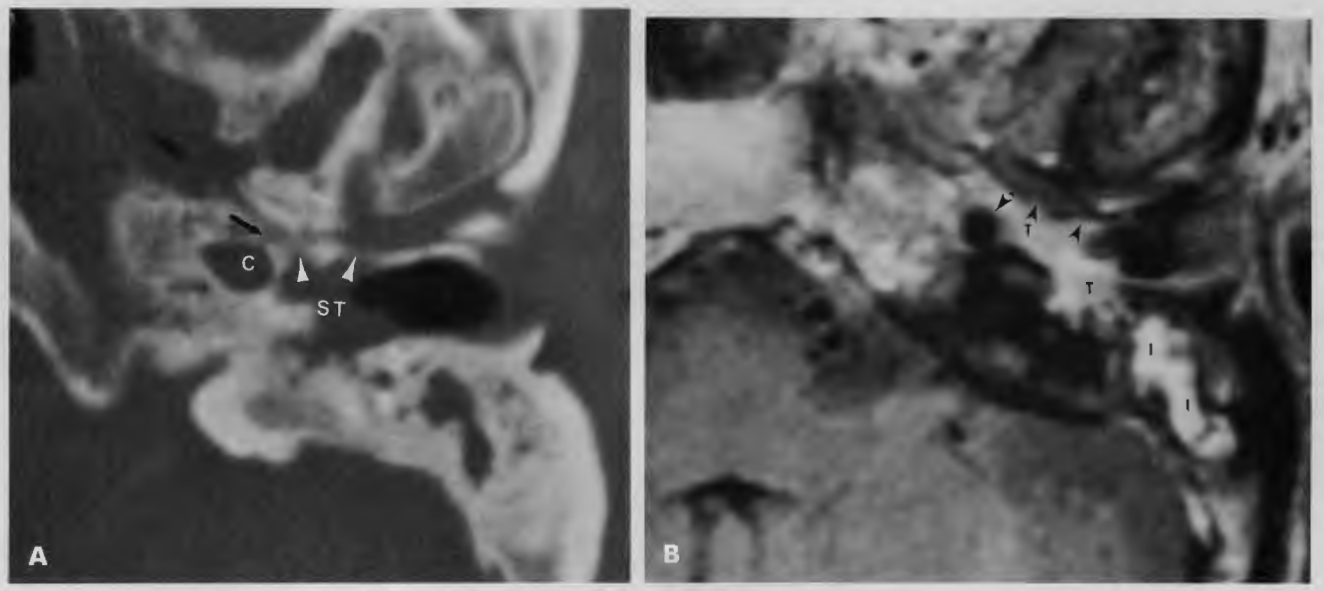

Figure 29-4. A patient with a long history of chronic middle ear disease and increasing ear pain. Exploratory tympanotomy and biopsy revealed squamous cell carcinoma of the middle ear. (*A*) Axial CT shows the middle ear filled with soft tissue (ST); this is a nonspecific finding. The bone surrounding the middle ear is markedly sclerotic and focally eroded (*arrowheads*); note, in particular, the focal erosion (*arrow*) between the bony eustachian tube and carotid canal (C). (*B*) A T1-weighted, contrast-enhanced axial MRI at the same level as the CT seen in *A*. Tumor (T) in the middle ear and mastoid was enhanced less than the inflammatory changes (I) in the mastoid. In particular, note the proximity of the tumor to areas of focal bone erosion seen in *A* (*arrowheads*).

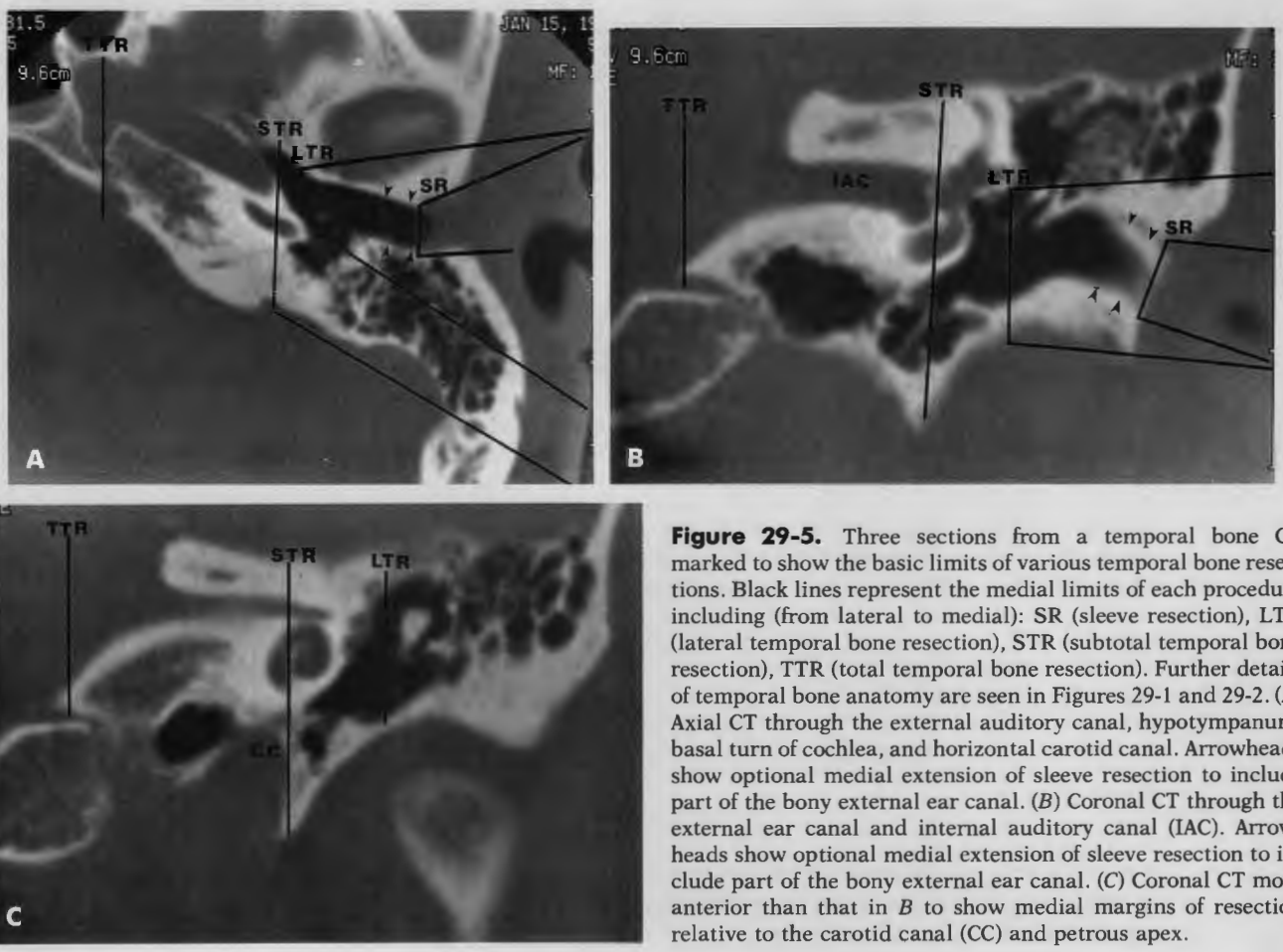

Figure 29-5. Three sections from a temporal bone CT marked to show the basic limits of various temporal bone resections. Black lines represent the medial limits of each procedure including (from lateral to medial): SR (sleeve resection), LTR (lateral temporal bone resection), STR (subtotal temporal bone resection), TTR (total temporal bone resection). Further details of temporal bone anatomy are seen in Figures 29-1 and 29-2. (*A*) Axial CT through the external auditory canal, hypotympanum, basal turn of cochlea, and horizontal carotid canal. Arrowheads show optional medial extension of sleeve resection to include part of the bony external ear canal. (*B*) Coronal CT through the external ear canal and internal auditory canal (IAC). Arrowheads show optional medial extension of sleeve resection to include part of the bony external ear canal. (*C*) Coronal CT more anterior than that in *B* to show medial margins of resection relative to the carotid canal (CC) and petrous apex.

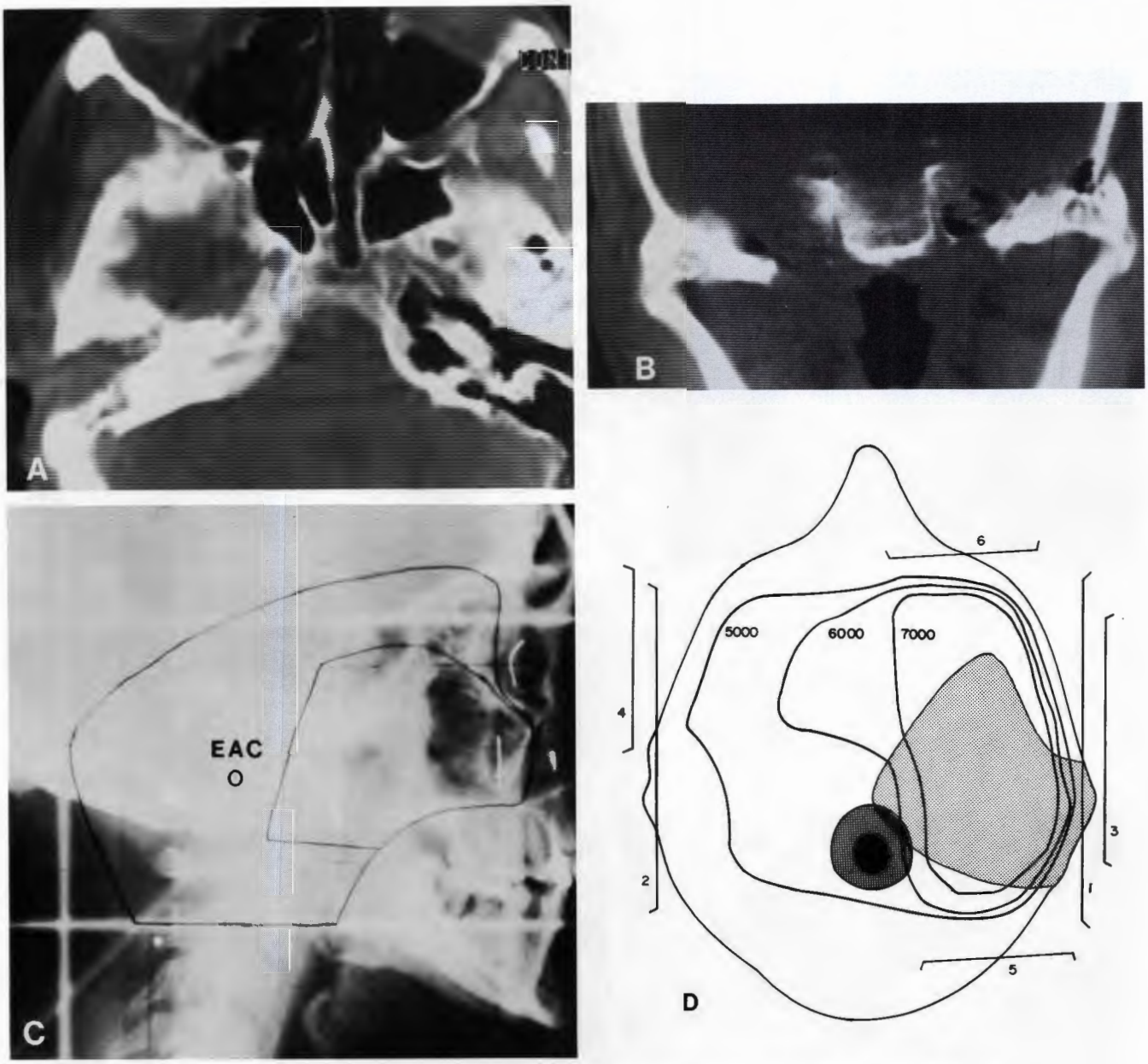

Figure 29-6. A 50-year-old man had a history of of chronic right middle ear infection of long duration. There was recent increased pain. Exploration revealed squamous cell carcinoma of the middle ear. (*A*) Axial CT scan. There is destruction of the right petrous apex and floor of the middle cranial fossa. The foramen lacerum is enlarged. The temporal bone is sclerotic. (*B*) Coronal CT. Note destruction of the right petrous apex and floor of the middle cranial fossa. (*C*) Simulator planning film. The large portal corresponds to portals 1 and 2 in *D*. The smaller portal corresponds to portal 4 (EAC, external auditory canal). (*D*) Isodose distribution. The tumor extended within 1 cm of the brain stem near the foramen magnum. It was necessary to deliver approximately 2000 cGy to the right eye in order to limit the dose to the brain stem (*black*). The minimum tumor dose was 6000 cGy over 8½ weeks, but the gross disease probably received 7000 cGy.

Portal	Energy	Field Size (cm)	Wedge Angle	Given Dose (cGy)
1	8 MV	12 × 9	Open	4300
2	17 MV	12 × 9	Open	2000
3	8 MV	9 × 9	Open	500
4	17 MV	6 × 5	60	1200
5	17 MV	5 × 9	30	1300
6	17 MV	5 × 9	30	1300

(*E*) Positioning device (see Chap. 14 for details of preparation). There was no evidence of disease at 10 years; the patient was working full time.

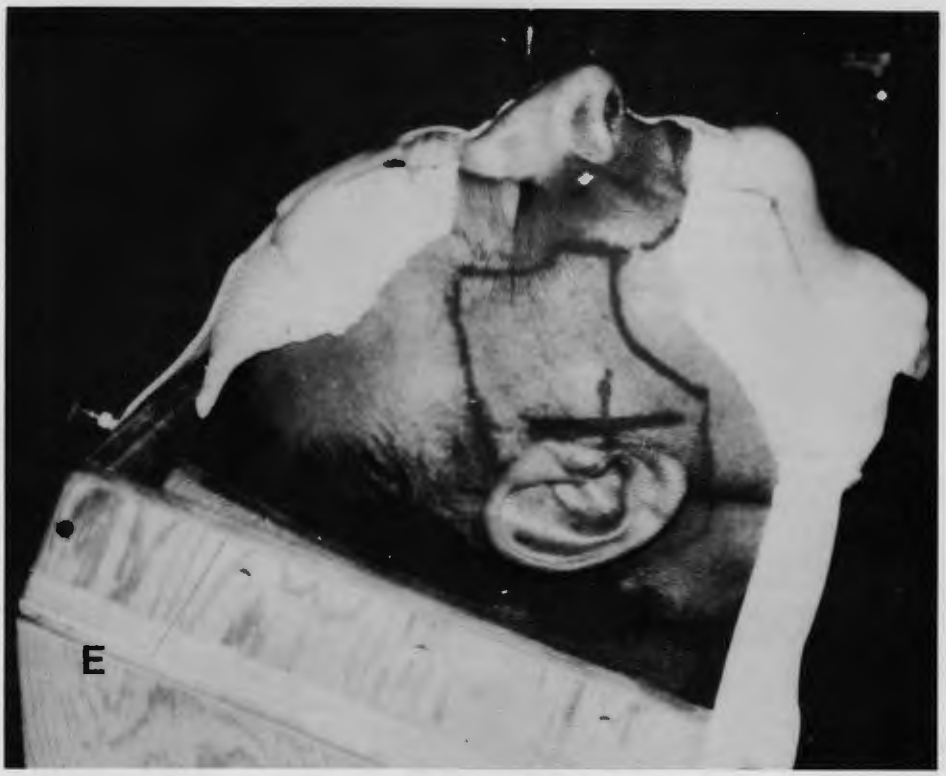

Figure 29-6. (*Continued*)

nal auditory canal results in a large external auditory meatus. Hearing is generally preserved, and the pinna remains intact. Lateral temporal bone resection results in a mild to moderate conductive hearing loss and creates a mastoid bowl that requires cleaning at intervals.

Middle Ear

Before the description of subtotal temporal bone resection in 1954,[15] treatment consisted of either radical mastoidectomy (and thus incomplete removal of tumor) followed by postoperative radiation therapy, or piecemeal removal of tumor and temporal bone and postoperative radiation therapy. Radical mastoidectomy alone is not sufficient treatment for the advanced lesions of the external auditory canal; it has been tried by Lewis[11] and at the M.D. Anderson Hospital[8] and was successful in only 2 of 23 patients from both series.

If there is more than minimal involvement of the middle ear, the application of the principle of en bloc cancer surgery requires a subtotal temporal bone resection. Extension of tumor to the petrous apex, cavernous sinus, internal auditory canal, internal carotid artery, middle or posterior cranial fossa, C1, C2, or the basioccipital bone is a relative contraindication. The resection of tumor in these areas may fail to be complete and may be associated with excessive surgical morbidity or mortality.

The subtotal temporal bone resection describes removal of the entire temporal bone excluding the petrous apex with the internal carotid artery serving as the medial margin of resection (see Fig. 29-5). The technique is a combination extracranial–intracranial procedure. The patient first has a temporal craniotomy, and the temporal lobe and dura are retracted to expose the petrous portion of the temporal bone. Minimal involvement of the dura can be excised with the specimen. The sigmoid sinus is exposed and may be resected if necessary when the opposite sinus is patent. The petrosal segment is fractured through the labyrinth at a level just lateral to the carotid canal, and the specimen is removed. The defect may be filled with a muscular flap. Extension of disease to the parotid, the mandible, or the neck may dictate an in-continuity parotidectomy, partial mandibulectomy, or radical neck dissection. In highly selected cases of tumor involving the petrous apex, total temporal bone resection may be indicated. This procedure includes removal of the petrous apex and requires resection of the intracranial carotid artery (see Fig. 29-5). Preoperative carotid balloon occlusion and xenon-enhanced CT blood flow studies are useful in predicting the relative safety of this resection.[5] In addition, removal of the petrous apex may require management of cavernous sinus tumor involvement or vascular tears secondary to the resection.

Subtotal or total temporal bone resections imply complete loss of hearing, temporary or persistent balance disturbance due to loss of the semicircular canals, complete facial paralysis, and some degree of difficulty with mastication.

Irradiation Technique

External Auditory Canal

Lesions confined to the external auditory canal and adjacent structures are usually treated with a pair of superior and inferior angled wedge portals, sometimes in conjunction with a single ipsilateral portal. Mixed-beam or electron techniques would also produce a satisfactory and simpler technique. The incidental doses delivered to the spinal cord, brain stem, and brain are well within the

TABLE 29-1. Carcinoma of the External Auditory Canal: Surgical Series

Type of Treatment	Controlled/Treated				
	Conley and Novack[4] (5 y)	Lewis[11] (3 y)	M.D. Anderson Hospital[8] (3 y)	University of Florida (2 y)	Shih and Crabtree[18] (1 y)
Early—sleeve resection ± mastoidectomy	2/8	5/6	3/4	1/1	5/5
Late—temporal bone resection	0/2	11/13	3/4	1/1	No data

limits of tolerance. The treatment is fractionated at 180 to 200 cGy per day because of the underlying cartilage, bone, and central nervous system. Small lesions would receive 6000 cGy over 6 to 7 weeks, and larger lesions would receive 6500 to 7500 cGy. Reducing field techniques are employed. The preauricular, postauricular, and subdigastric nodes would fortuitously be encompassed by the irradiation plan.

Middle Ear

There is no standard portal arrangement for irradiation of lesions of the middle ear. Angled wedge fields may be used for the smaller lesions (see Chap. 30 for examples). Those lesions invading near the midline require highly individualized treatment planning. Because the apex of the temporal bone is within 2 cm of the brain stem, it is a technical nightmare to deliver the high dose required (7000 to 7500 cGy) to have a chance at cure for an advanced lesion (Fig. 29-6). The dose to the brain stem is at least 6000 cGy and possibly more, and the patient must accept a small risk of myelitis in the face of a uniform fatality from the neoplasm. If only a small portion of the brain stem/spinal cord receives 6000 cGy at 180 cGy per day, the risk of transverse myelitis is estimated at 1% to 5%, and, for a dose of 7000 cGy, the risk is considerable.

Combined Treatment Policies

Irradiation is added after operation for incomplete resection or for large lesions even when margins are considered to be free.

Management of Recurrence

A number of surgical successes have occurred after an unsuccessful full dose of irradiation.[4]

RESULTS OF TREATMENT

Results from several series by treatment and site of origin are listed in Tables 29-1 through 29-5.[2–4,6,8–11,18–20] Comparisons between institutions are full of hazards. Irradiation series often include lesions and patients not suitable for operation, surgical series often include irradiation failures, and there is no standard reporting method to separate external auditory canal from middle ear lesions.

Arriaga and coworkers[2] reported on 24 previously untreated squamous cell carcinomas of the external auditory canal managed by surgical resection and postoperative irradiation. Patients were operated on between 1974 and 1987 and had a 2-year minimum follow-up (see Table 29-5). All three patients with disease limited to the external auditory canal were cured. Six of the 15 patients with tumors eroding bone of the external auditory canal, involving the mastoid or the middle ear, were cured. Middle ear involvement and positive margins were associated with a higher risk of local recurrence. Only one of six patients with advanced lesions (dura, petrous apex, soft tissue extensions) were cured. There were two operative fatalities.

Early carcinomas of the cartilaginous auditory canal are equally well treated by irradiation or sleeve resection of the canal. More advanced carcinomas of the external auditory canal with minimal involvement of the tympanic cavity may be managed by lateral temporal bone resection with postoperative irradiation added as needed

TABLE 29-2. Carcinoma of the External Auditory Canal: Radiation Therapy Series

Study	Follow-Up (y)	Controlled/Treated
Boland and Paterson[3]	5	9/11
University of Florida	2	4/5*
Lederman and coworkers[9]	5	6/25

* One failure subsequently salvaged by subtotal temporal bone resection for ultimate control in 5 of 5.

TABLE 29-3. Carcinoma of the Middle Ear: Surgical Series

Study	Follow-Up (y)	Controlled/Treated
Conley and Novack[4]	5	2/11
Lewis[11]	3	3/12
Jesse and coworkers[8]	3	1/3

TABLE 29-4. Carcinoma of the Middle Ear: Radiation Therapy Series

Study	Follow-Up (y)	Controlled/Treated
Holmes[6]	5	28/78 (36%)
Lederman and coworkers[9]	5	12/39 (31%)

or with irradiation alone in patients not suitable for operation.

For carcinomas of the middle ear, there seems to be a small advantage to surgical resection and postoperative irradiation in patients with lesions suitable for the operation; this treatment should produce about a 50% cure rate. The cure rate for middle ear lesions by irradiation alone, however, is approximately 33%, and fewer hazards occur, although they are not insignificant. Many patients treated curatively by irradiation would not be suitable for surgical resection because of extension to the middle cranial fossa or apex of the petrous bone, or cranial nerve involvement (other than the facial or vestibulocochlear nerve). Therefore, subtotal temporal bone resection with dural involvement or total temporal bone resection does not appear to be of significant curative benefit.[2] If there is doubt about resectability, it seems prudent to proceed with a full course of radiation therapy and to reserve an operation for persistence.

FOLLOW-UP POLICY

Radiation failures may occasionally be salvaged by an operation. Biopsy should be performed when an ulcer fails to heal or if there is persistent mass or pain. Exploration of the middle ear and mastoid may be required for diagnosis. Baseline CT or MRI should be obtained, and follow-up studies should be ordered periodically for comparison.

COMPLICATIONS OF TREATMENT

Surgical Treatment

The operative mortality should be low for partial temporal bone resection. Patients may complain of dizziness in cold water due to the increased exposure of the semicircular canals created by the defect.

Conley and Novack[4] reported a 60-day operative mortality of 27% (3 of 11) for temporal bone resection; 8 of the 11 patients had had prior radiation therapy or surgery. In experienced hands, the operative mortality has diminished, but it still remains a significant deterrent to the novice.

Hemorrhage may be considerable, and ample blood must be available for transfusion.

The carotid may be injured, possibly resulting in hemiplegia.

Cerebrospinal leak may lead to meningitis or brain abscess. Removal of the semicircular canals results in vertigo and loss of equilibrium; the patient usually recovers in 4 to 6 weeks, although a degree of unsteadiness may persist for several months and is more severe in the dark. Loss of the facial nerve requires a tarsorrhaphy or insertion of a gold weight in the upper lid to prevent corneal exposure. The pinna may be lost with resection of the larger lesions; a prosthesis may be constructed if desired (see Chap. 9).

Radiation Therapy

External Auditory Canal

Serous otitis develops in at least half of the patients, and some require pressure-equalization tubes for relief. Soft tissue or bone necrosis may occur adjacent to the external auditory canal. Hearing should not be seriously affected unless a chronic otitis develops.

Middle Ear

Holmes[6] reported three cases of central nervous system damage (two fatal) and seven cases of bone necrosis in a group of 78 radically irradiated patients. Treatment for bone necrosis was débridement and antibiotics. One patient at the University of Florida developed multiple cranial nerve palsies but lived for 5 years free of disease.

Combined Treatment

Wang[20] reported five cases of osteonecrosis of the temporal bone in 20 patients treated by excision and postoperative radiation therapy; three of the patients survived more than 5 years. A dose equivalent to or greater than 7000 cGy over 7 weeks was correlated with complications.

TABLE 29-5. Carcinoma of the External Auditory Canal and Middle Ear: Treatment by Surgery and Radiation Therapy

	Controlled/Treated						
Location	M.D. Anderson Hospital[8] (3 y)	Wang[20] (5 y)	University of Florida (2 y)	Sørenson[19] (5 y)	Conley and Novack[4] (5 y)	Shih and Crabtree[18] (1 y)	Arriaga[2] (2 y)
External auditory canal							
Early stage	No data	4/4	No data	No data	1/1	No data	3/3
Late stage	0/1	3/11	No data	No data	1/1	7/10	7/21
Middle ear	0/3	4/8	1/2	5/11	No data	No data	No data

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30

CHEMODECTOMAS (GLOMUS BODY TUMORS)

RODNEY R. MILLION, NICHOLAS J. CASSISI, ANTHONY A. MANCUSO, AND SCOTT P. STRINGER

Chemodectomas are a fascinating but uncommon group of low-grade malignancies that may originate anywhere glomus bodies are found. The lesions are uncommon before the age of 20, and there is a female predominance in some series. They occur in multiple sites in 10% to 20% of cases, especially in families with a history of this tumor.[48] Familial lesions are more likely to occur bilaterally and to be nonmetastasizing compared to sporadic lesions. Carotid body tumors are associated with conditions producing chronic hypoxia, such as living in areas of high altitude, and chronic hypoxemia, such as occurs in association with cyanotic heart disease. A few of the tumors demonstrate endocrine activity and produce symptoms similar to a pheochromocytoma or a carcinoid apudoma.

ANATOMY

The normal glomus bodies in the head and neck vary from 0.1 to 0.5 mm in diameter. An autopsy study showed a correlation between carotid body size and increased right ventricular weight secondary to emphysema.[9] Because of their small size, their total number and distribution in the head and neck remain speculative. Tumors arising from glomus bodies (ie, chemodectomas or nonchromaffin paragangliomas) occur most often from the carotid and temporal bone glomus bodies, with rare reports of tumors arising from the orbit, nasopharynx, larynx, nasal cavity, paranasal sinuses, tongue, jaw, and trachea.

The glomus bodies of the temporal bone require special mention in regard to their distribution, because the site of tumor development explains the different clinical pictures.

Guild[20] reported an average of 2.82 glomera per temporal bone with a range of 0 to 12. Because the glomera are so tiny, this realistically represents a minimum number. The temporal bone glomus bodies are not consistently found in any location but vary from person to person. The distribution of the glomus bodies in the temporal bone and along the cranial nerves near the base of the skull is shown in Figure 30-1. At least one half of the glomus bodies are found in the general region of the jugular fossa and are located in the adventitia of the superior bulb of the internal jugular vein. The remainder are distributed along the course of Jacobson's nerve (a branch of the glossopharyngeal nerve). Approximately 20% of all temporal bone glomus bodies lie in the tympanic canaliculus, and approximately 11% lie in relation to the cochlear promontory. A few glomus bodies are located adjacent to the descending part of the facial canal.

The carotid bodies are located in relation to the bifurcation of the common carotid; orbital glomus bodies are located in relation to the ciliary nerve.

The vagal bodies are found either within or adjacent to the ganglion nodosum of the vagus nerve. They are rarely located below the ganglion in relation to the vagus nerve. The superior laryngeal glomus bodies are situated in the false cord/aryepiglottic fold region, and the inferior laryngeal glomus bodies usually lie lateral to the cricoid cartilage. Their position is variable.[29]

PATHOLOGY

Chemodectomas are histologically benign tumors that resemble the parent tissue and consist of nests of epithelioid cells within stroma containing thin-walled blood

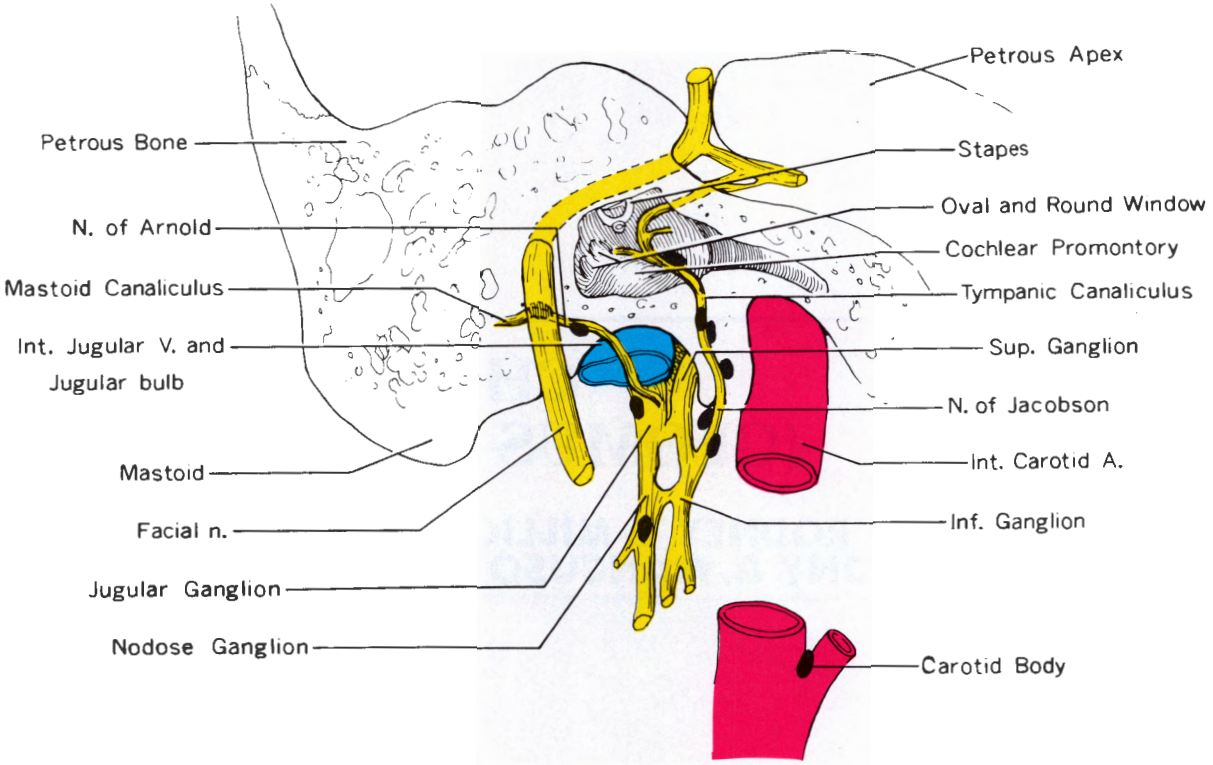

Figure 30-1. Anatomic location of glomus bodies in the temporal bone. Approximately half of the glomus bodies are located in the region of the superior jugular bulb of the internal jugular vein.

vessels and nonmyelinated nerve fibers. The tumor mass is well circumscribed, but a true capsule is not seen. Dense fibrous bands occur in some tumors and account for the firmness of some masses. The histologic appearance varies, depending on the relative amount of epithelioid and vascular tissue present. The criterion of malignancy is based on the clinical progress of the disease rather than on the histologic picture. Chemodectomas without cellular atypia may metastasize to regional nodes or to distant organs. Metastases are infrequent, probably occurring in less than 5% of cases.

Endocrine activity has been reported in a few head and neck chemodectomas.[11] Lawson[28] concluded that the glomus cell is a modified neuroblast of neural crest origin with the ability to synthesize biogenic monoamines in tissue culture and, therefore, is a true neurocrine cell. Although the glomus bodies and glomus tumors are normally nonchromaffin, areas of positive staining cells may be seen, which suggests the presence of catecholamines. The presence of serotonin (5-hydroxytryptamine) has also been demonstrated by histochemical staining. The infrequency of clinically detectable endocrine activity is probably related to the sparseness of the secretory granules in these tumors.

PATTERNS OF SPREAD

Chemodectomas usually grow slowly, and it is usual to have a history of symptoms for a few years and occasionally for 20 years or longer.

Primary Spread

Carotid Body Tumors

Carotid body tumors are located at the bifurcation of the common carotid and, as they expand, they tend to displace and encircle the internal and external carotid vessels (Fig. 30-2).[12] The tumor begins in the adventitia of the artery and initially derives its blood supply from the vasa vasorum. An accessory blood supply may come from branches of the vertebral artery and the ascending pharyngeal artery.[50] The tumor is usually closely adherent to the wall of the carotid adjacent to its vascular pedicle, and there may be thinning of the arterial wall due to pressure by the mass. Large masses extend toward the cervical spine, the base of the skull, the angle of the mandible, and the parapharyngeal space and its contents.

Temporal Bone Tumors

Glomus tympanicum lesions tend to be small when diagnosed because they produce symptoms early in their course. Tumor may involve the ossicles, tympanic membrane, mastoid, external auditory canal, semicircular canals, and the facial, Jacobson's, and Arnold's nerves (Fig. 30-3).

Glomus jugulare tumors invade the jugular fossa and may go on to involve the petrous apex, jugular vein, middle ear, and middle and posterior cranial fossae (Fig. 30-4; see also Fig. 4-1). Cranial nerves V through XII and the sympathetic chain are frequently involved. Spector and

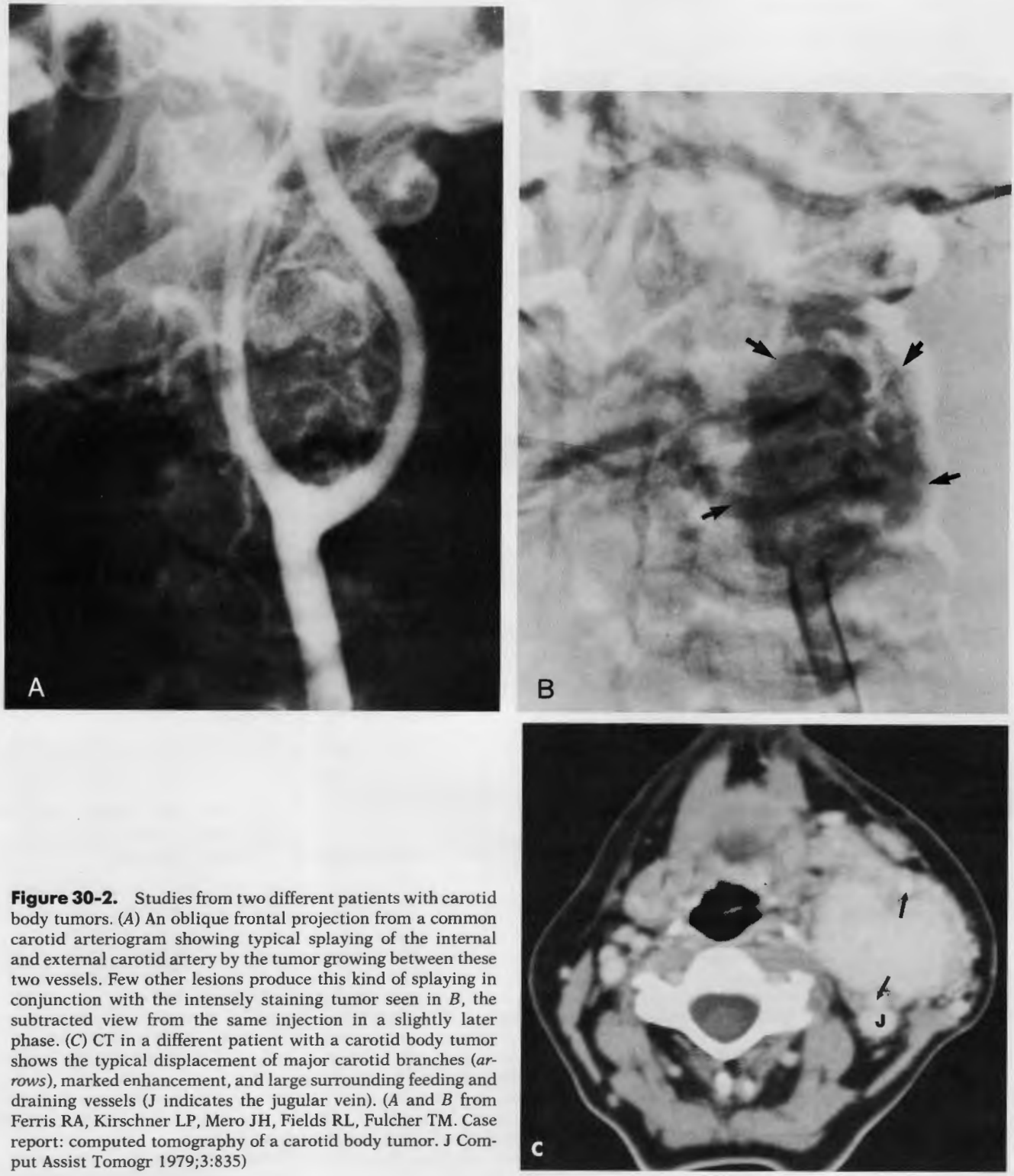

Figure 30-2. Studies from two different patients with carotid body tumors. (*A*) An oblique frontal projection from a common carotid arteriogram showing typical splaying of the internal and external carotid artery by the tumor growing between these two vessels. Few other lesions produce this kind of splaying in conjunction with the intensely staining tumor seen in *B*, the subtracted view from the same injection in a slightly later phase. (*C*) CT in a different patient with a carotid body tumor shows the typical displacement of major carotid branches (*arrows*), marked enhancement, and large surrounding feeding and draining vessels (J indicates the jugular vein). (*A* and *B* from Ferris RA, Kirschner LP, Mero JH, Fields RL, Fulcher TM. Case report: computed tomography of a carotid body tumor. J Comput Assist Tomogr 1979;3:835)

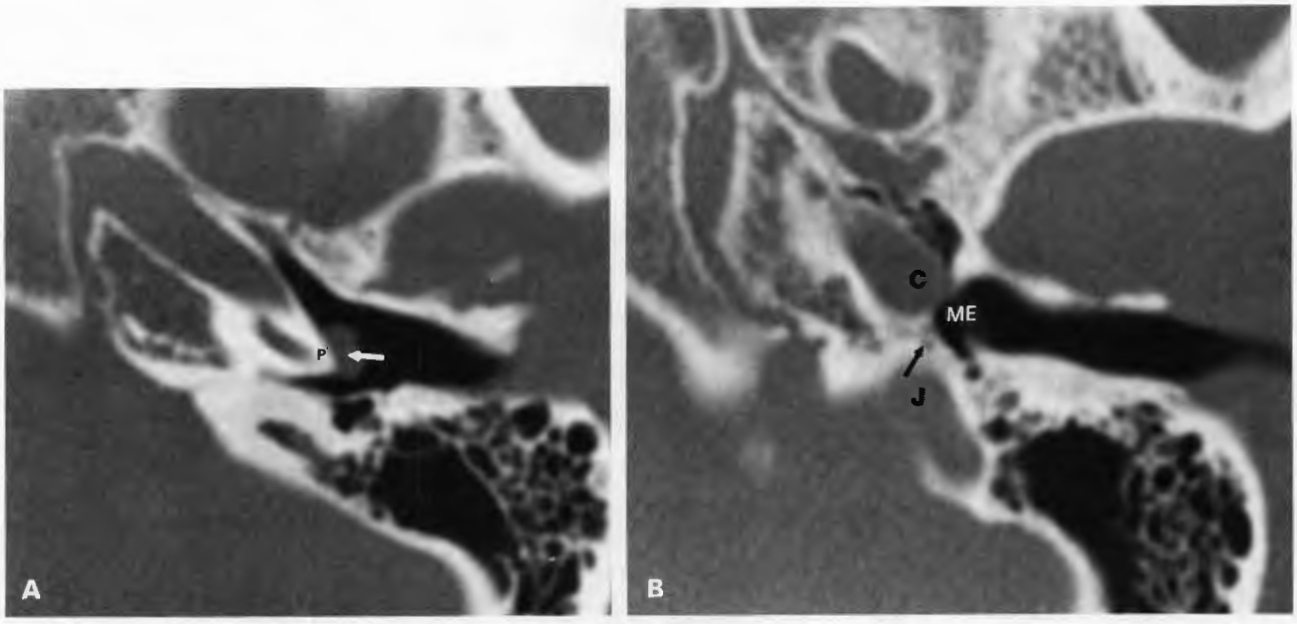

Figure 30-3. This patient presented with pulsatile tinnitus and a reddish mass visible behind the tympanic membrane. (*A*) Axial CT done without contrast infusion shows an approximately 5-mm mass (*arrow*) centered on the promontory (P). (*B*) A section made several millimeters lower than that in *A* shows the carotid artery in its normal position (C). The mass is no longer visible in the middle ear (ME). The tympanic canaliculus (*arrow*) and jugular fossa (J) are normal. *Comment:* This study showed findings consistent with a glomus tympanicum tumor limited to the middle ear. Noncontrast CT alone was enough to confirm the clinical diagnosis and assure the referring surgeon that this was not the top of a larger paraganglioma either extending into the inferior tympanic canaliculus or growing upward from the jugular fossa. This tumor was simply removed by way of a tympanotomy-type approach.

coworkers[42] reported a 15% incidence of intracranial extension.

The remaining temporal bone glomus tumors are mainly along the tympanic canaliculus and do not have a specific name affixed to them. They tend to spread along the course of the tympanic canaliculus, eventually reaching the middle ear superiorly and the jugular fossa inferiorly (Fig. 30-5).

Glomus Vagale Tumors

Initially, glomus vagale tumors tend to invade the vagus nerve and produce a mass in the poststyloid parapharyngeal space (Fig. 30-6). As growth proceeds, the carotid is displaced and eventually may be invaded. Cranial nerves IX through XII and the sympathetic chain are invaded eventually. The mass may grow inferiorly

Figure 30-4. A middle-aged woman with a glomus jugulare tumor. (*A*) Axial CT shows the typical, very aggressive destruction of the bony margins in the region of the jugular fossa. Note that the tumor erodes the bone (*arrows*) just medial to the facial canal (*arrowhead*). Medially, the tumor has thinned the lateral wall of the hypoglossal canal (*open arrow*). Also note the extent of erosion at the junction of the sigmoid sinus and jugular bulb (*white arrowheads*). (*B*) Contrast-enhanced T1-weighted MRI at a plane nearly the same as that of the CT section in *A*. The enhancing tumor (T) can be seen just posterior to the carotid artery (C), just lateral to the hypoglossal canal (H), and extending intracranially into the cisterns around the cerebellum. (*C*) CT made through the level of the hypotympanum shows bone erosion along the expected course of the inferior petrosal sinus in the region of the petroclival fissue; bone destruction can be seen in this region (*arrows*). There is also abnormal soft tissue in the middle ear (*arrowhead*) and within the mastoid. The region of the sigmoid sinus (S) is not obviously abnormal. (*D*) T1-weighted contrast-enhanced MRI in the axial plane at approximately the same level as the CT seen in *C*. This shows enhancing tumor within the inferior petrosal sinus (*arrow*) confirming the suspicion on the CT. Enhancing tumor is also seen in the middle ear (*arrowheads*) and in the sigmoid sinus (S). T2-weighted images showed that the changes in the mastoid (M) were related to mucosal thickening and fluid (see Fig. 4-1). (*E*) The best overall perspective of this lesion is seen on this sagittal view made through the plane of the jugular fossa and jugular vein. Tumor (T) fills the jugular fossa (*arrow*) and extends inferiorly within the jugular vein; its inferior tip is visible within the lumen of the vein (*arrowhead*). Its extension into the low posterior fossa (*open arrow*) is also obvious. *Comment:* This patient was favoring surgery as a treatment of choice based on evaluations at another institution. After demonstration of tumor involving a very extensive area of the skull base as well as growing within the inferior petrosal sinus, the patient elected radiotherapy rather than surgery as her primary means of treatment.

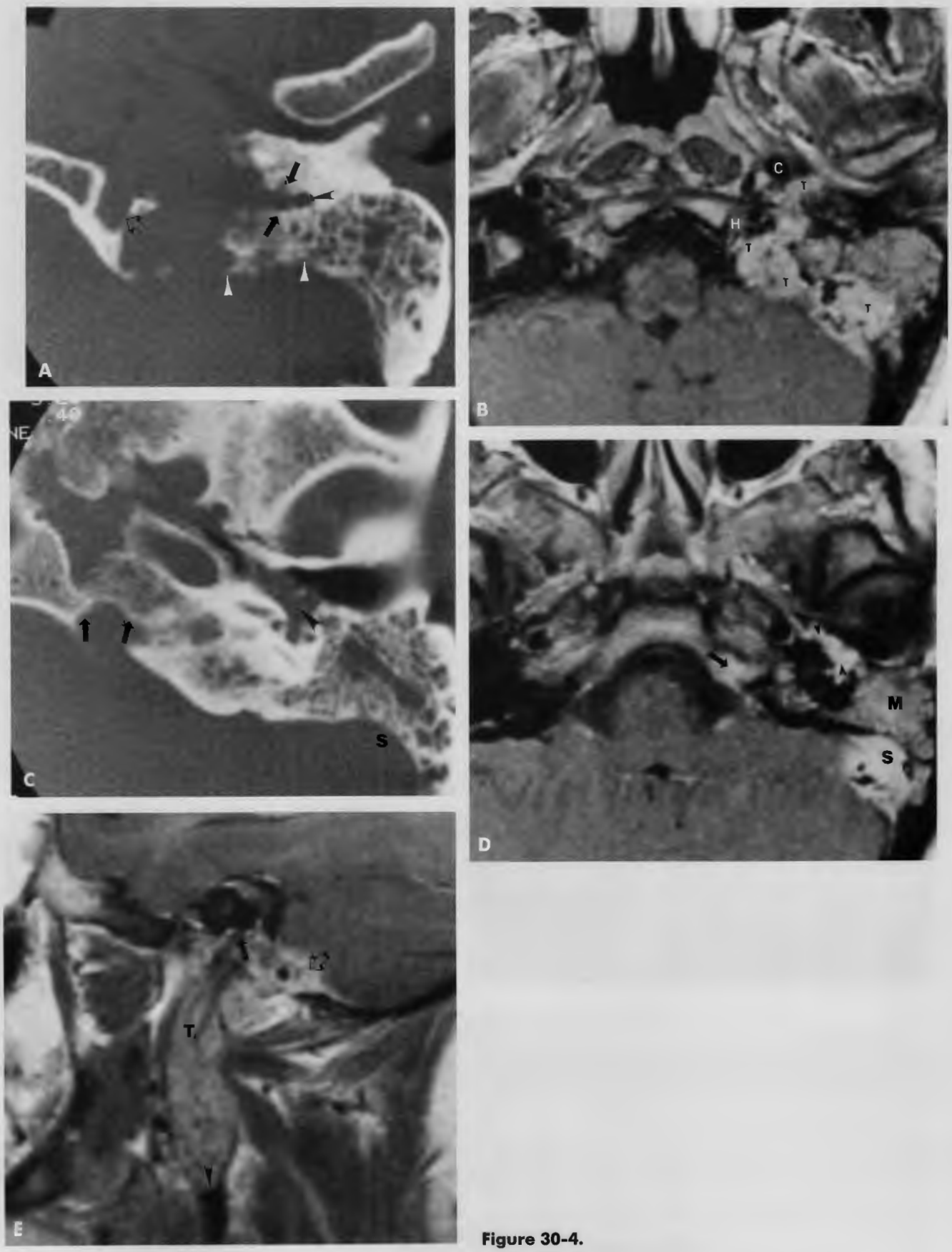

Figure 30-4.

Figure 30-5. Just as the patient in Figure 30-4, this patient presented with pulsatile tinnitus and a reddish mass visible behind the ear drum in the hypotympanum. (*A*) Noncontrast CT was done and showed a lobulated mass in the hypotympanum (M). The carotid artery (C) was in its normal position, and the bone of the carotid canal was intact. There is definite evidence, however, of erosion of the bone (*arrowheads*) between the carotid canal and jugular fossa (J). Note also the defect in the mastoid (*white arrow*); this resulted from surgery at another institution. The patient was approached for what was believed to be a tumor limited to the middle ear. The surgery was stopped because of uncontrollable bleeding experienced during subtotal resection of the mass. (B) A coronal section from the noncontrast CT clearly shows the tumor filling the middle ear (T) extending along the expected course of the tympanic canaliculus (*arrow*). (*C*) A coronal section from T2-weighted MRI at approximately the same plane as that seen in the CT shown in *B*. The tumor (T) is centered in the region of the tympanic canaliculus. The mass grows down into the jugular bulb, and there is fairly clear interface between the jugular vein (V) and the inferior aspect of the mass (*arrowheads*). The extension into the middle ear is obvious (*open arrow*) and easily distinguished from the much brighter obstructive changes in the mastoid antrum (M). *Comment:* This tumor started either in the dome of the jugular fossa or within the tympanic canaliculus and extended both superiorly and inferiorly. A more complete imaging evaluation before the initial surgery (at another institution) could have avoided the subtotal resection of the lesion. Failure to recognize extension of predominantly middle ear tumors along the tympanic canaliculus may be a reason for persistent or recurrent tumor after what appears to be a complete resection.

toward the carotid bifurcation and displace the tail of the parotid gland. Base of skull invasion is rarely seen.

Laryngeal Tumors

Sixteen glomus body tumors in the supraglottic larynx and one tumor along the lateral surface of the thyroid cartilage have been reported.[52] The tumors average 3 to 4 cm in size. Metastatic disease may be found in the lymph nodes.

The supraglottic lesion usually presents as a smooth, submucosal, cystic-appearing mass in the aryepiglottic fold–false vocal cord area. Subglottic and tracheal cases are reported.[29]

Lymphatic Spread

Lymphatic metastases from temporal bone tumor are rare but are occasionally reported for vagal body, carotid body, and laryngeal chemodectomas. An upper neck mass may be an inferior extension of a temporal bone or a glomus vagale tumor rather than a lymph node metastasis.

Distant Metastases

Distant metastases have been reported, usually to the lung and skeleton. The risk is greater for carotid body and vagale tumors than for temporal bone tumors. The reported incidence of regional and distant metastases from carotid body tumors varies widely. Zbaren and Lehmann[53] reviewed the literature and estimated a risk of approximately 10%. About half of the metastases were to regional lymph nodes, and half were to distant sites. Considering the frequency of jugular vein invasion by temporal bone tumors, the rate of distant spread is small. Bone metastases are usually lytic but may be sclerotic.[42]

CLINICAL PICTURE

Symptoms may be present from a few months to many years before diagnosis; the average is 3 to 4 years. Tumors usually occur after the age of 20, but a few have been reported between the ages of 10 and 20.

Glomus tumors may be associated with an endocrine syndrome similar to that of a pheochromocytoma or, more rarely, a functioning carcinoid tumor. Hypertension may be cyclical. Control of the tumor by surgery or radiation therapy may improve or eliminate the hypertension.[28]

Patients with carcinoid syndrome have a history of recurring bouts of explosive diarrhea, headaches, flushing, and hypertension.[11]

Medullary carcinoma of the thyroid and pheochromocytoma may occur in association with chemodectomas.

Carotid Body Tumors

Presenting Symptoms

The most common presenting symptom is an asymptomatic, slow-growing mass in the upper neck near the bifurcation of the carotid. Large masses may encroach on the parapharyngeal space and produce dysphagia, pain, and cranial nerve palsies. A carotid sinus syndrome may occur as a result of the pressure of the mass.

Physical Examination

On examination, the mass usually lies deep to the sternocleidomastoid muscle and is tethered to surrounding structures. The borders of the mass are discrete. It is difficult to distinguish a small carotid body tumor from a normal carotid bulb. Fixation occurs in large tumors that extend to the spine and base of the skull. A submucosal bulge may be seen in the tonsillar area. A bruit may be heard. Steady compression of the mass may reduce its size; it rebounds when the pressure is released. This maneuver is discouraged, because it may initiate a syncopal attack due to pressure on the carotid sinus. Ipsilateral enlarged lymph nodes may represent regional spread.

Temporal Bone Tumors

Presenting Symptoms

Because there is variation in the distribution of glomus bodies, the initial symptoms and signs depend on the site of origin.

Patients with tumors arising in or near the middle ear present with an insidious conductive hearing loss, pulsatile tinnitus, vertigo, and headache.

Patients with lesions developing in or around the jugular fossa develop headache that is often pulsatile and referred to the orbit or temple. Cranial nerves V through XII and the sympathetic nerves become affected.

When lesions develop in the facial canal, patients present with facial nerve symptoms. Otorrhea and hemorrhage may occur when tumor breaks through into the external auditory canal.

Intracranial extension is usually associated with multiple cranial nerve palsies, severe headache, and symptoms and signs of increased intracranial pressure. Extension to the posterior cranial fossa may produce ataxia, pulsatile occipital headache, and paralysis of cranial nerves V through XII. Massive tumors may invade the middle cranial fossa and result in paralysis of cranial nerves III through VI and retroorbital pain; proptosis occurs with posterior orbital invasion.

Physical Examination

A characteristic blue–red mass may be seen bulging the tympanic membrane or actually occupying the external auditory canal. Brown[4] described a diagnostic test he termed the "pulsation sign." An ear speculum fitted with an air bulb is inserted into the external auditory meatus. As the pressure is gradually increased, the mass at first shows increased pulsation, but then the pulsations cease and the tumor blanches; when the pressure is released, the color and pulsations return. A mass may be seen or felt in the upper neck between the mandible and mastoid and, at times, may be large. Lymph node metastases are rare.

Cranial nerves V through XII and the sympathetic nerves may show varying degrees of neurologic loss. Papilledema occurs with increased intracranial pressure. Proptosis and visual loss are reported in advanced lesions.[42]

Glomus Vagale Tumors

Vagal chemodectomas often present with hoarseness, but may present with only an asymptomatic, slowly enlarging upper neck mass at the angle of the mandible or a mass bulging into the lateral pharyngeal wall. They are sometimes mistaken for parotid masses. Paralysis of the vagus is common; cranial nerves XI and XII and the sympathetic nerves may be involved.

Laryngeal Chemodectomas

The symptoms are similar to carcinoma of the supraglottic larynx: hoarseness or voice change, dysphagia, sore throat, ear pain, stridor, and a mass in the neck.

They may present with persistent throat pain, which is a major symptom, and the lesions may be very small and difficult to diagnose. These lesions have a propensity for regional and distant spread, and early recognition and diagnosis are important. The painful symptoms may be present for many years before the diagnosis is established.

Figure 30-6. Examples of glomus vagale tumors in two different patients. (*A*) CT several centimeters below the skull base in a patient presenting with pulsatile tinnitus. There is a mass centered in the poststyloid parapharyngeal space. Note the displacement of the styloid process (*arrow*). (*B*) A sagittal T1-weighted image done without contrast infusion from an MRI of the patient whose CT was shown in *A*. The tumor (T) begins below the jugular fossa (*arrowhead*). Large vessels (*arrow*) within the tumor are typical of the large vessels seen in paragangliomas. (*C* and *D*) Views from subselective injections of the occipital artery made during the embolization of this lesion. The view before embolization shows typical hypervascularity and staining of a paraganglioma. After embolization, tumor supply from this vessel was completely obliterated. This lesion was removed with less than 1000 ml of blood loss and without creating any cranial nerve deficits. (*E*) A second patient had a glomus vagale tumor removed at another institution. This MRI was done in follow-up and to serve as a gross screening evaluation for other paragangliomas. This T1-weighted image done after infusion of paramagnetic contrast medium showed a small enhancing mass (*arrow*) between the jugular vein (J) and internal carotid artery (*arrowhead*). (*F*) Angiography confirmed the presence of a small glomus vagale tumor (*arrow*) on the side opposite the original surgery. *Comment:* CT and MRI may be used for observation of patients with treated paragangliomas. A combination of imaging and angiography is required for confidently excluding multiple tumors. Imaging alone can usually exclude tumors 2 cm or larger; however, if MRI is used as a screening tool, smaller lesions can easily be missed in the region of the jugular fossa because of the extensive variation in the appearance of the skull base in this location.

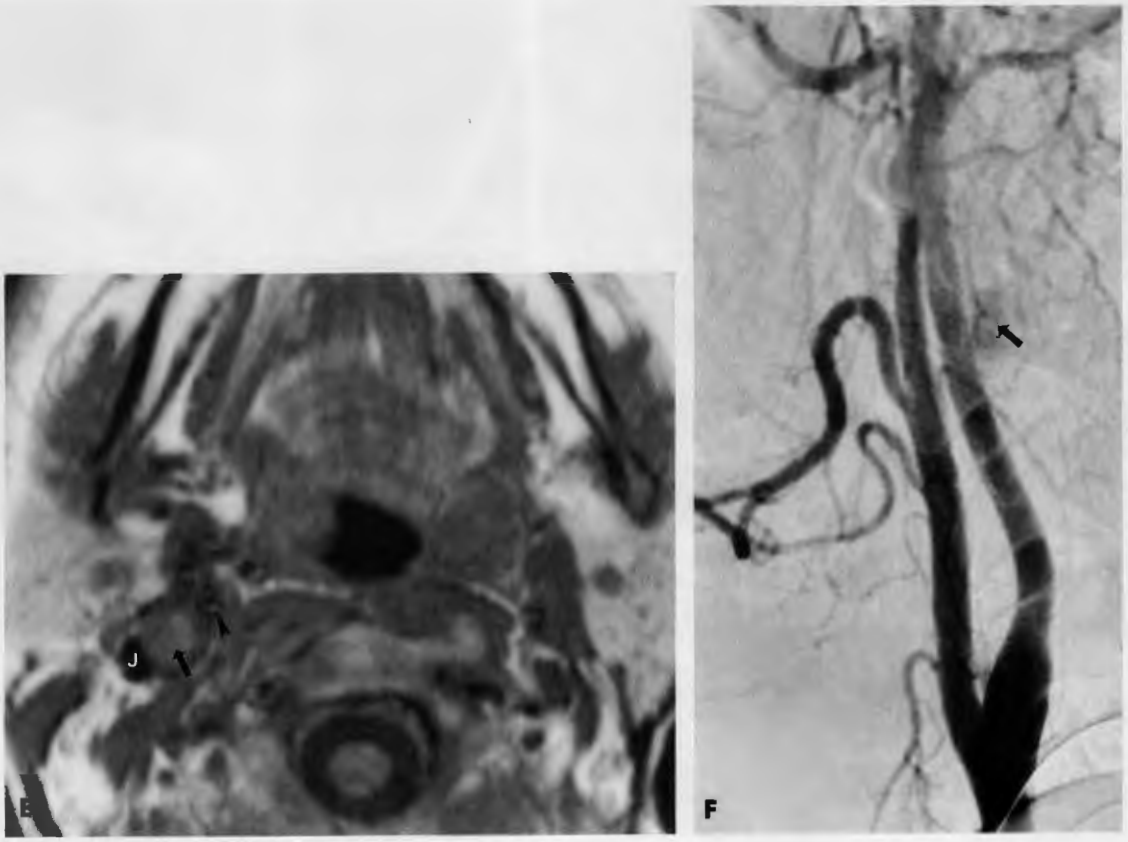

Figure 30-6. (*Continued*)

Orbital Chemodectomas

These rare lesions present with exophthalmos, diplopia, and loss of vision.

METHODS OF DIAGNOSIS AND STAGING

Imaging

At the University of Florida, computed tomography (CT) is preferred as the initial study in most patients presenting with pulsatile tinnitus with or without a middle ear mass. One must evaluate the bone detail around the jugular fossa, carotid canal, and other portions of the temporal bone to make an accurate diagnosis and determine the extent of a chemodectoma. The lack of cortical bone detail, variations in the marrow content of the skull base, and flow-related artifacts in this region make magnetic resonance imaging (MRI) difficult to use in smaller lesions. MRI has advantages in the evaluation of patients with possible vascular lesions as well as cranial nerve deficits and certainly may be used as a complementary study whenever necessary. MRI is particularly well suited to confirming the vascular nature of the tumor (potentially eliminating a diagnostic angiogram) and for follow-up of larger (greater than 2 cm) tumors treated with radiotherapy. In extensive lesions, three-dimensional reconstruction of CT data or multiplanar MRI may aid in planning treatment.[30]

Angiography is used to confirm the diagnosis in questionable cases. Typical imaging features combined with typical angiographic findings are equivalent to a biopsy. If either study is atypical, histologic confirmation may be necessary (see the following section). Preoperative embolization may be used as an aid to surgery.

Technique of Examination

Lesions of the temporal bone should be studied with 1.5- to 2-mm sections on CT and 2- to 5-mm sections on MRI. CT scans should be reconstructed with both bone and soft tissue algorithms. It is feasible to do an MRI examination to study the full intracranial and extracranial extent of the lesion in combination with a noncontrast CT for evaluating bony changes. In lesions below the skull base, MRI alone may be adequate. Noncontrast CT is sufficient for evaluating tumors confined to the middle ear. Axial and coronal sections should always be done in tumors of the temporal bone or those potentially spreading to the skull base.

MRI or CT may be used to image glomus vagale or carotid body tumors as well as the uncommon orbital and laryngeal tumors. Dynamic contrast-enhanced CT studies have been used to aid in differential diagnosis; however, if the diagnosis is in question, angiography is required.

Imaging of the Normal Anatomy

The anatomy relevant to temporal bone lesions is presented in Chapter 29, and that related to spread below

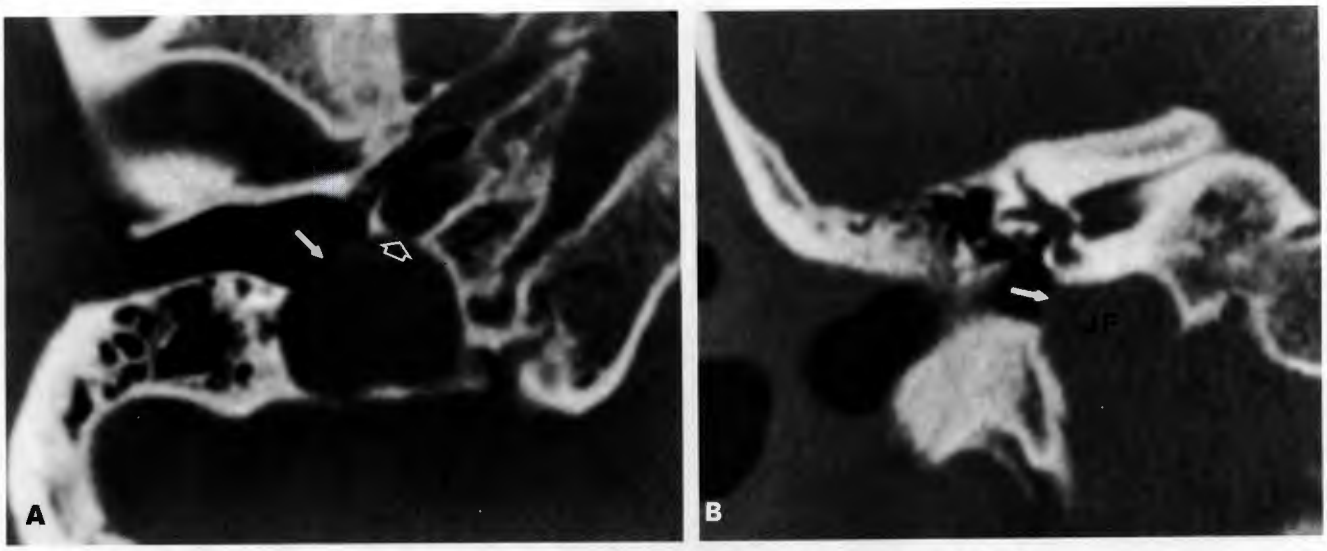

Figure 30-7. This patient had pulsatile tinnitus and a bluish mass visible behind the tympanic membrane. (*A*) Axial CT made through the region of the jugular fossa (JF). The fossa is enlarged; however, its walls are smooth and, for the most part, well corticated (*arrowheads*). There is no bone visible where the bulb lies adjacent to the hypotympanum (*arrow*), and there is an area of dehiscence between the bulb and carotid canal (*open arrow*). (*B*) Noncontrast CT in the coronal plane shows the well-corticated and smooth outline of the large jugular fossa (*JF*). Note that no obvious bone is present between the large jugular bulb and the hypotympanum (*arrow*). *Comment:* Glomus jugulare tumors always produce irregular destruction of the walls of the jugular fossa. Typical examples are seen in Figure 30-4, (see also Fig. 4-1). Smaller paragangliomas erode the bone around the inferior tympanic canaliculus; an example of this is shown in Figure 30-5. Occasionally, unschooled interpreters mistake a large jugular fossa, which is a normal variant, for one eroded by a paraganglioma; the two have obviously distinctive appearances. If a patient is to be treated for paraganglioma, the CT must demonstrate a typical erosive pattern of bone destruction and the diagnosis must be confirmed by MRI or angiography. Occasionally, a schwannoma produces smooth-walled enlargement of the jugular fossa. Exclusion of a schwannoma would require MRI, but this should be done only in patients with appropriate symptomatology because the vast majority of "large jugular bulbs" are normal anatomic variants.

the skull base in the parapharyngeal space and deep neck is presented in Chapters 6 and 23. Normal anatomic variation in the jugular fossa is common. A high or large jugular bulb may be mistaken for a glomus jugulare tumor. Flow-related artifacts in the jugular fossa on MRI may also lead to the mistaken impression that the normal jugular bulb is a tumor. Careful CT evaluation of the bony margins of the jugular fossa and familiarity with these anatomic and artifactual pitfalls help avoid such error (Fig. 30-7).

Indications for Study

DIAGNOSIS AND SEARCH FOR MULTIPLE LESIONS. The combination of typical CT and MRI findings with typical angiographic features is virtually diagnostic of a paraganglioma and equivalent to biopsy. In questionable cases of a mass arising in the usual locations for a paraganglioma, angiography may be necessary to confirm the diagnosis. On the other hand, hypervascular lesions arising at sites atypical for chemodectomas may be misdiagnosed as a chemodectoma. In possible jugular fossa lesions, a CT scan, done in the axial and coronal planes and processed using a bone algorithm, is essential for diagnosis. A pattern of aggressive erosion is consistent with paraganglioma (see Fig. 30-4), whereas an enlarged jugular fossa with smooth walls is a normal variant (see Fig. 30-7) or nerve sheath tumor. Bone erosion also helps in the differential diagnosis of lesions under 2 to 3 cm, which do not always show the typical branching flow voids indicative of a high-flow lesion with large feeding and draining vessels (see Fig. 30-5).

Angiography is necessary as an adjunct to CT and MRI to look for multiple chemodectomas (see Fig. 30-6).

EVALUATION OF THE EXTENT OF THE LESION. Glomus tympanicum tumors typically grow into the middle ear cavity from their site of origin on the promontory (see Fig. 30-3). Bone erosion is not a prominent feature of these lesions when they present at an early stage and are confined to the middle ear (see Fig. 30-3).

Clinically, a mass in the middle ear may be thought to be a glomus tympanicum tumor and may, in reality, be the superior aspect of a tumor beginning in the inferior tympanic canaliculus or jugular fossa. The hallmark of a glomus jugulare tumor is bone destruction extending centripetally from the jugular fossa. The pattern of bone is destructive in nature, and the bony margins are indistinct (see Fig. 30-4). They grow inferiorly within the soft tissues of the poststyloid parapharyngeal space or within the lumen of the jugular vein. MRI is the easiest and

most accurate means of assessing the extent of tumor growth in the jugular vein (see Figs. 30-4 and 4-1).

Tumors grow intracranially from the jugular fossa region. At first, the growth is extradural, but in advanced lesions, the tumors may extend into the cerebellopontine angle cistern and higher. Growth into or along the sigmoid and inferior petrosal sinus may cause foci of tumor to be located far from the central nidus of tumor in the jugular fossa (see Fig. 30-4). The full extent of a glomus vagale tumor is best evaluated on CT or MRI. It typically is centered in the poststyloid parapharyngeal space (see Fig. 30-6*A*). The styloid and its related muscles are displaced anterolaterally. The carotid artery is pushed anteriorly or anteromedially. The lesion may encroach on but not truly involve the prestyloid parapharyngeal space. If the lesion is in the masticator space, some other diagnosis should be entertained because this is highly atypical. These lesions frequently grow laterally and inferiorly from the poststyloid parapharyngeal space and may present as a "parotid mass" while actually displacing the tail of the gland. They can reach the carotid bifurcation and mimic a carotid body tumor. Glomus vagale tumors usually are diagnosed before they reach the skull base (see Fig. 30-6*B*).

Carotid body tumors grow mainly between the internal and external carotid artery at the bifurcation. Their extent is easily defined on MRI or CT (see Fig. 30-2).

Laryngeal tumors usually present as a submucosal mass on the aryepiglottic fold. The diagnosis is usually not anticipated before biopsy, but if marked enhancement is observed on a CT or MRI image in a patient with a clinically submucosal mass, laryngeal paraganglioma should be a prime consideration.

EMBOLIZATION AS AN ADJUNCT TO THERAPY. Diagnostic angiography may be necessary as a prelude to therapeutic embolization (see Fig. 30-6*A* through *D*). Endovascular techniques are not a definitive means of treatment and are used basically to reduce surgical blood loss. Endovascular procedures on chemodectomas should be attempted only by experienced people because of the risk of embolic complications both in the carotid and vertebral circulations.

FOLLOW-UP IMAGING. MRI or CT is suitable for follow-up of treated tumors. A baseline study should be obtained about 12 to 16 weeks after therapy to ensure complete healing or resolution of radiation-induced changes in surrounding tissues. Patients treated with radiotherapy frequently have a substantial residual mass. Minimal to less than 50% reduction in the tumor volume is most often the case, although 50% to 100% reductions are reported. Areas of gross necrosis and calcification (dystrophic) may be present after radiotherapy but are uncommon in untreated benign tumors. The residual mass usually continues to concentrate intravenously administered iodinated (on CT) or paramagnetic (on MRI) contrast material. Loss of the internal pattern of flow voids seen on MRI and a steadily decreasing signal (due to fibrosis) on MRI may also be taken as signs of successful radiotherapy.

Postoperatively, there should be no obvious residual mass if gross total resection was completed. Dural enhancement in and near the operative bed is commonly present up to 1 year (and sometimes longer) after surgery in the absence of recurrent or residual tumor. As a reactive change, this remains stable or resolves with time.

Staging

The surgical staging system recommended by Fisch and Mattox[13] is outlined in the section on surgical treatment. Patients treated with radiation therapy at the University of Florida are considered to have an early lesion when there is little or no bone destruction and an advanced lesion when there is extensive bone destruction or there are cranial nerve deficits. Tumors recurring after prior treatment are usually advanced. A 24-hour urine sample may be examined for vanillylmandelic acid (VMA) and metanephrines if hypertension is present, and for 5-hydroxyindoleacetic acid (5-HIAA) if a carcinoid picture is present.

TREATMENT

Selection of Treatment Modality

Although chemodectomas have a low potential for metastatic spread and a slow growth pattern, if unchecked they may cause major disability and eventual death. It may be appropriate to recommend no active treatment in selected nonprogressive, stable cases, but the great majority should be treated.

Complete surgical excision in properly selected cases is curative. If excision is incomplete and residual tumor remains, the patient may be observed for evidence of regrowth before adding further therapy or irradiation may be added immediately, particularly for those in whom symptoms persist.

Irradiation halts disease progression, results in varying degrees of tumor regression, and alleviates many annoying symptoms with doses of 4000 to 4500 cGy. Although concern is often expressed in the surgical literature that irradiation produces only temporary growth restraint, several radiotherapy series include follow-up for 15 to 30 years without regrowth.[44] A stable palpable or radiographic abnormality is of less concern to the patient than to the doctor. No avalanche of late recurrences after radiotherapy has materialized. The risk of a radiation-induced sarcoma appearing many years later is far less than the operative mortality.

Temporal Bone Tumors

Surgical excision is recommended for small lesions confined to the tympanic cavity. The remainder are managed initially by radiotherapy, and surgery is reserved for the few patients whose lesions progress after radiotherapy. It is unwarranted to risk extensive surgery for temporal bone tumors considering the good results for radiotherapy.

Reviews by Kim and coworkers[26] of over 200 patients and by Springate and associates[44] showed that the recurrence rate after radiation therapy for temporal bone chemodectomas was at least as good as after surgery, if not better. Most of the failures noted in early radiation therapy series were probably due to inadequate treatment volume (ie, geographic miss). In some cases, examination of the temporal bone after radiation therapy has shown either no definable tumor or a few microscopic residuals. In the majority of patients, the tumor mass regresses, but stable remnants may be seen for years. Success in these patients is equated with the lack of tumor regrowth and

permanent improvement in signs and symptoms including reversal of cranial nerve deficits in a few cases. The moderate doses of radiation, 4000 to 4500 cGy over 5 to 5½ weeks, should not compromise a subsequent operation should it be needed.

Carotid Body Tumors

Small lesions (1 to 5 cm) may be removed successfully with little risk to the patient. However, if ligation or replacement of the carotid vessels is anticipated or if a large lesion is fixed or unresectable because of size, radiation therapy is the preferred initial treatment. These lesions are identical histologically to temporal bone chemodectomas, and the response to radiation is similar. There are scattered reports of complete regression of the mass, whereas most lesions show moderate to no regression. There are anecdotal cases in which patients have lived many years after radiation therapy with no recurrence or progression, even though there was a residual tumor mass. The doses in some cases were well below the accepted level of 4000 to 4500 cGy, and the lack of immediate regression is not necessarily tantamount to therapeutic failure.[51] Stroke and cranial nerve damage may occur after operation of the larger lesions. The dose of radiation, 4000 to 4500 cGy, should not compromise a subsequent operation should it be needed.

Glomus Vagale Tumors

Radiation therapy is preferred as the initial treatment.

Surgical Treatment

The staging system commonly used for glomus temporale tumors is that proposed by Fisch and Mattox,[13] which is based on CT and angiography. Class A tumors originate along the tympanic plexus on the promontory and are limited to the middle ear. They are commonly referred to as glomus tympanicum tumors. Class B tumors invade the middle ear and mastoid, eroding the bone of the hypotympanum but sparing the jugular bulb; these arise in the inferior tympanic canaliculus. Class C tumors originate from the jugular bulb and destroy the overlying cortical bone. The typical spread patterns from this point were described previously. The extent of involvement of the carotid canal and artery is used to stratify class C tumors into four subgroups. Class D indicates the intracranial involvement of a tumor, and this group is also further subdivided by the size of the tumor and extent of dural involvement.

Most glomus tympanicum tumors (class A) may be removed by way of a retroauricular incision and the elevation of a tympanomeatal flap. The addition of a mastoidectomy and the removal of the inferior bony tympanic ring are required for complete resection of glomus hypotympanicum tumors (class B). Postoperative conductive hearing loss may be minimized with appropriate ossicular reconstruction techniques.

If surgery is to be considered for initial tumor removal or for radiation failure with glomus jugulare lesions (class C and D), an infratemporal fossa approach (type A as described by Fisch and Mattox) is most appropriate. Subtotal petrosectomy and anterior transposition of the facial nerve are used to expose the infralabyrinthine and apical temporal bone, the mandibular fossa, and the posterior infratemporal fossa.

When an adequate work-up indicates that the most likely diagnosis is a carotid body tumor, hypertension, if present, should be treated. A standard neck incision is made in a skin crease at the level of the carotid bulb, and the carotid sheath and its contents are identified. The tumor mass is usually lying at the crotch of the internal and external carotid arteries, often displacing these vessels. Marked drops in blood pressure and bradycardia can be avoided by injecting the bulb area with lidocaine (Xylocaine). Troublesome bleeding can be avoided by using the bipolar electrode before excising the mass. The mass is removed, preserving the carotid arteries.

Irradiation Techniques

Treatment planning starts with collation of tumor extent from the arteriogram (Fig. 30-8) or contrast-enhanced CT or MRI; properly done and interpreted studies should show the extent of tumor accurately. Small to moderate-sized temporal bone lesions are treated by superior and inferior angled wedged portals to reduce the dose to the midline and avoid an exit dose to the eye (Fig. 30-9).[8,46] Large temporal bone lesions, especially those that extend near the midline, usually require opposed lateral portals weighted 2 : 1 or 3 : 2 to the ipsilateral side. Small glomus vagale lesions can usually be encompassed with an angled wedge pair aimed in the anteroposterior axis. Large vagale lesions require individualized planning. Carotid body tumors can usually be managed with a wedge pair aimed anteroposteriorly.

Multiple series show nearly 100% long-term control with doses greater than 4000 to 4500 cGy and an *adequate treatment volume.* The current treatment plan is 4500 cGy over 5 weeks with 180 cGy per fraction, to a generous tumor volume. All portals should be treated each day. There is no evidence that the larger lesions require a higher dose.

Tumor-related symptoms may begin to improve during the first week of treatment, and the tumor mass, if visible, may show a decrease in size. Frequently, however, the regression rate slows, and a persistent mass is usually seen at the completion of treatment. In some cases, there is no measurable reduction in mass size during the course of radiation therapy. Some patients eventually show complete gross disappearance of visible or palpable tumor, but many have a persistent, stable gross lesion. Nausea and vomiting are uncommon side effects with the use of 180 cGy per fraction. The patient has temporary hair loss in the entrance and exit areas beginning about the third week. The hair should regrow over a period of 2 to 4 months but may show a slightly different texture or color. Cranial nerve deficits may partially or completely heal in a few cases, especially those in which the cranial nerve dysfunction is of short duration before treatment.

Management of Recurrence

Temporal Bone Tumors

The diagnosis of recurrence is often delayed because of the inaccessibility to examination. Baseline MRI or CT should be obtained for reference. CT is adequate if MRI is

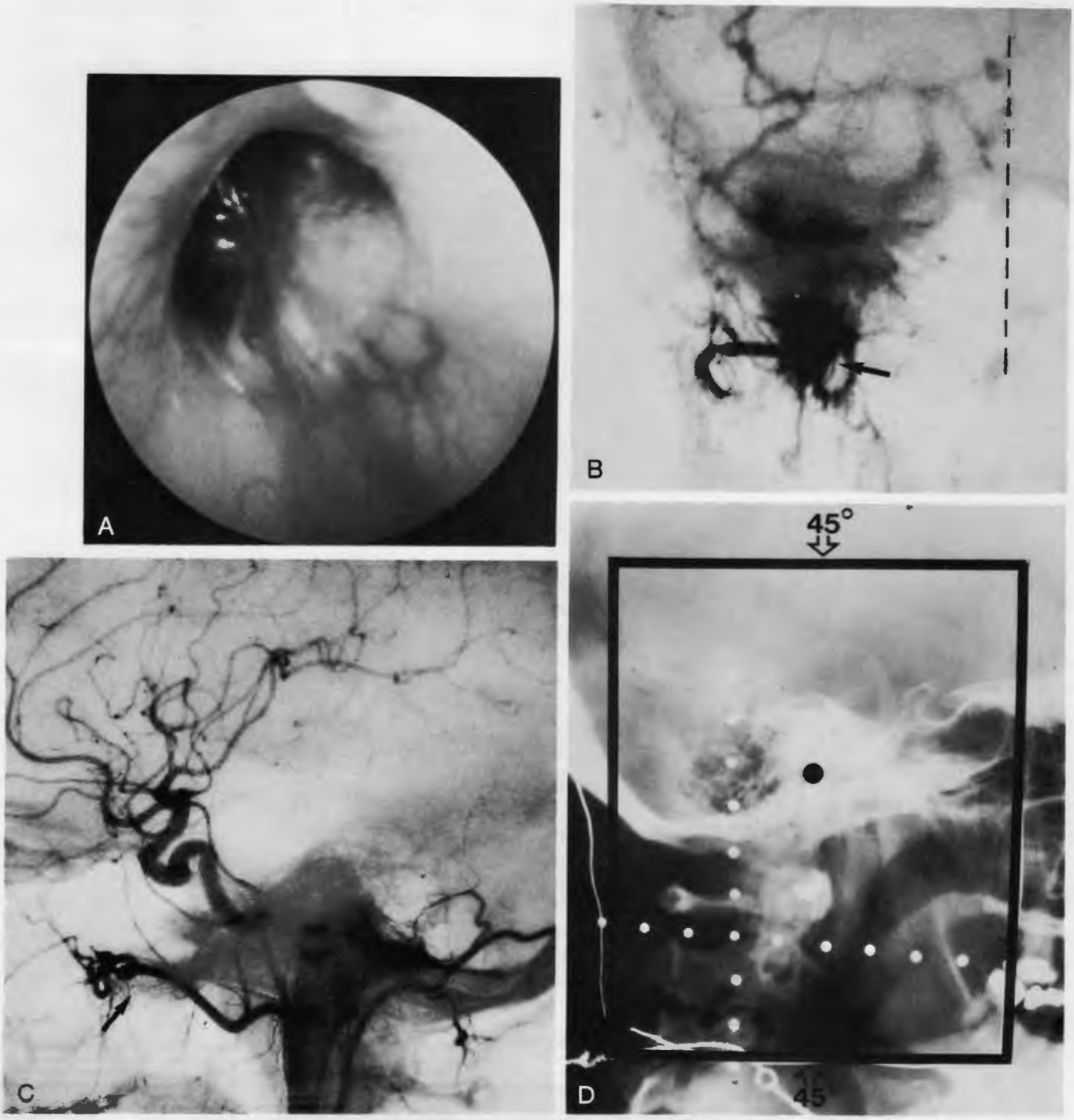

Figure 30-8. Treatment planning for a moderately advanced chemodectoma of the temporal bone. The treatment volume should be generous to avoid missing tumor that may not show on arteriogram or CT. (*A*) Blue–red mass bulging into external auditory canal (photograph taken through a fiberoptic nasoscope). (*B*) Anteroposterior arteriogram (subtraction technique). The mass extends to within 1 cm of the midline and 3 to 4 cm below the jugular fossa (*arrow*). (*C*) Arteriogram, lateral view. Note anterior extension of tumor (*arrow*). (*D*) Treatment planning film. Black dot locates the external auditory canal. Compare location of anterior and posterior borders to the arteriogram (*B* and *C*). Superoinferior angled beams were used. (See Fig. 30-9*B* for representative isodose distribution.)

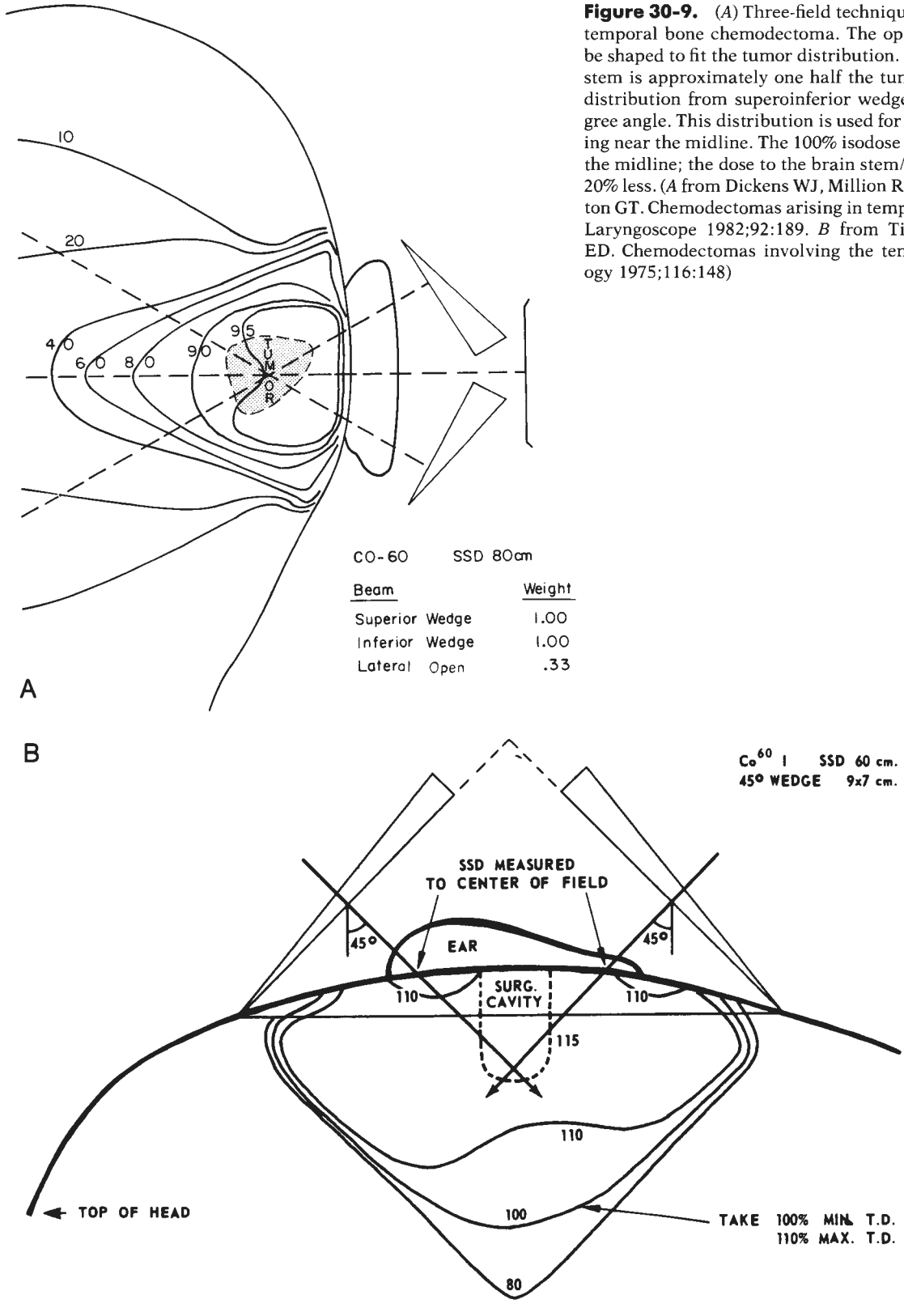

Figure 30-9. (*A*) Three-field technique for relatively small temporal bone chemodectoma. The open lateral portal can be shaped to fit the tumor distribution. The dose to the brain stem is approximately one half the tumor dose. (*B*) Isodose distribution from superoinferior wedge portals with 45-degree angle. This distribution is used for large tumors extending near the midline. The 100% isodose is within 1 to 2 cm of the midline; the dose to the brain stem/spinal cord is 10% to 20% less. (*A* from Dickens WJ, Million RR, Cassisi NJ, Singleton GT. Chemodectomas arising in temporal bone structures. Laryngoscope 1982;92:189. *B* from Tidwell TJ, Montague ED. Chemodectomas involving the temporal bone. Radiology 1975;116:148)

TABLE 30-1. Temporal Bone Chemodectomas: Local Control of Previously Untreated Lesions in 25 Patients

Treatment Group	Stage		Local Control/Treated
	Local	Advanced	
Radiotherapy alone	6	9	15/15
Surgery alone	6	0	6/6
Surgery plus postoperative radiotherapy*	0	4	4/4

* Radiotherapy given for incomplete resection.
(Friedland JL, Mendenhall WM, Parsons JT, Million RR, Cassisi NJ. Chemodectomas arising in temporal bone structures. Head Neck Surg 1988;10:S53)

not available and may be preferred if the tumor is small and lies predominantly within the confines of the temporal bone. There is no standard interval for repeat imaging.

Regrowth of tumor after proper irradiation is uncommon, and the diagnosis must be made only after complete reevaluation and evidence of progression of symptoms or an enlarging mass. Pulsatile tinnitus may persist after irradiation because of incomplete regression of the vascular component of the tumor.[32,33]

Documented recurrence after operation is usually treated by irradiation; the complication rate in this group is higher than for those treated initially by irradiation. Recurrence after irradiation should be treated by operation if feasible; if operation is not possible, reirradiation may be considered. The potential for a complication would be significant, but in the face of advancing neoplasm, the risk would probably be acceptable.

Carotid Body Tumors

Recurrence of carotid body tumors after excision is related to the size of the initial lesion; in some series, the recurrence rate is substantial. Management of recurrence is individualized, but radiation therapy should be considered in the treatment planning.

RESULTS OF TREATMENT

Temporal Bone Tumors

Radiation Therapy

Reliable indications of successful treatment of a chemodectoma of the temporal bone structures include improvement in symptoms, return of cranial nerve function, and absence of disease progression with long-term follow-up. Chemodectomas in some cases show persistent evidence of tumor mass, presumably the vascular component, after irradiation.

Friedland and coworkers[14] updated the University of Florida radiation therapy results for patients treated with radiation therapy between 1964 and 1984. Follow-up was more than 5 years for 75% and more than 10 years for 39%. The control rates are shown according to treatment group in Tables 30-1 and 30-2. Five patients were free of progression for over 15 years. There were 57 cranial nerve defects before radiotherapy; 5 resolved completely, 14 partially resolved, and 2 became worse.

Konefal and coworkers[27] of the Washington University School of Medicine reported their radiation therapy results for 26 patients with chemodectomas treated between 1961 and 1983. Seventeen patients were irradiated for localized lesions, and, in all 17, the lesions were controlled. Seven patients had extensive disease, and radiation was able to control the disease in five. Cummings and associates[7] reported the Princess Margaret Hospital results for 45 patients for temporal bone chemodectomas treated with 3500 cGy in 15 fractions between 1958 and 1978. Median duration of follow-up was 10 years. Three had a symptomatic recurrence of their disease. One recurrence was successfully managed by excision, and two were retreated with symptomatic control. No patient died of uncontrolled glomus tumor. Tinnitus was completely relieved in 30 of 38 patients; vertigo, ear discharge, bleeding, and pain were completely relieved in all patients; and 37 of 40 patients reported that their hearing loss either remained stable or partially improved. Cranial nerve deficits remained stable but rarely completely disappeared.

The results for radiation therapy alone published between 1965 and 1988 for patients treated between 1932 and 1983 were compiled by Springate and associates[44] (Table 30-3). The control rate was 94%.

TABLE 30-2. Temporal Bone Chemodectomas: Local Control of Recurrent Lesions in Seven Patients

Prior Treatment Elsewhere	Treatment at University of Florida	Stage		Local Control/Treated
		Local	Advanced	
Surgery alone	RT	2	2	4/4
Surgery plus postoperative radiotherapy	RT	0	3	2/3

(Friedland JL, Mendenhall WM, Parsons JT, Million RR, Cassisi NJ. Chemodectomas arising in temporal bone structures. Head Neck Surg 1988;10:S53)

TABLE 30-3. Temporal Bone Chemodectomas: Local Control With Radiotherapy Alone After Biopsy or Radiotherapy as Salvage Therapy After Surgery

Institution	Local Control/Treated
Grubb and Lampe,[18] University of Michigan, 1965	11/11
Fuller et al.,[15] Mayo Clinic, 1967	33/34
Hudgins,[23] Baylor, 1972	9/9
Silverstone,[39] Mount Sinai, 1973	5/5
Arthur,[1] Queen Elizabeth, 1977	19/20
Gibbin and Henk,[17] University Hospital of Wales, 1978	12/14
Kim et al.,[26] University of Virginia, 1980	15/17
Cole,[6] Geisinger, 1977	18/20
Cummings et al.,[7] Princess Margaret Hospital, 1984	34/36
Dickens et al.,[8] University of Florida, 1982	15/15
Hatfield et al.,[22] Massachusetts General Hospital, 1972	4/4
Thomsen et al.,[45] Aarhus, Denmark, 1975	8/10
Reddy et al.,[36] University of Kansas, 1983	9/9
TOTAL	191/204 (94%)

(Springate SC, Weichselbaum RR. Radiation or surgery for chemodectoma of the temporal bone: a review of local control and complications. Head Neck 1990;12:305)

The results for patients treated initially with radiation therapy alone, or with preoperative or postoperative radiation therapy, are given in Table 30-4. The control rate was 91%.[44]

Schwaber and colleagues[38] reported a case of a catecholamine-producing glomus tumor that did not show any change in tumor size or in catecholamine secretion in 20 months of follow-up after treatment with 4750 cGy.

One patient at the University of Florida with hypertension and multicentric chemodectomas had minimal tumor regression and minimal improvement in hypertension after radiotherapy.

Surgery

Eight published series of patients treated surgically for glomus tympanicum and jugulare tumors between 1932 and 1985 were reviewed by Springate and coworkers[44] (Table 30-5). The local control rate for 405 patients was 86%.

The treatment results for 53 patients with glomus tympanicum tumors were reported by Jackson and coworkers.[25] There were no known recurrences or complications in this group of localized lesions.

Carotid Body Tumors

The rate of control is related to the tumor size and spread. The rate of control for complete surgical excision is very good. Incomplete removal is followed by local

TABLE 30-4. Glomus Tympanicum and Jugulare Chemodectomas: Local Control With Radiation Therapy With or Without Surgery

Institution	Dates	Tumor Dose (cGy)	Local Control/Treated	Follow-Up
Hatfield et al.,[22] Massachusetts General Hospital, 1972	1935–1965	1500–4500	13/16	Mean 9.7 y
Konefal et al.,[27] Washington University, 1987	1961–1983	4600–5500	21/23	Mean 10.5 y
Friedlond et al.,[14] University of Florida, 1987	1964–1984	3750–5640	19/19	3–18 y
Tidwell and Montague,[46] M.D. Anderson, 1975	1948–1970	4250–5000	16/17	4–18 y
Cole,[6] Geisinger Medical Center, 1977	1953–1975	2090–5700	20/22	3 mo–16 y
Cummings et al.,[7] Princess Margaret Hospital, 1984	1958–1978	3500 cGy/3 wk	42/45	3–23 y
Newman et al.,[34] University of California (San Francisco), 1973	1952–1969	4600–5500	6/6	18 mo–7 y
Simko et al.,[40] University of Washington, 1977	1960–1975	2800–6500	11/14	Mean 7.7 y
Kim et al.,[26] University of Virginia, 1980	1932–1978	1300–6200	26/30	1/30 y
Grubb and Lampe,[18] University of Michigan, 1965	1939–1963	2000–5100	14/14	1 mo–10 y
Fuller et al.,[15] Mayo Clinic, 1967	pre-1965	3000–3600	49/56	Median 5–10 y
Hudgins,[23] Baylor, 1972	1964–1971	4000–5000	9/9	1–7 y
Maruyama,[31] University of Minnesota, 1972	pre-1972	3000–6000	12/14	Not stated
Silverstone,[39] Mount Sinai, 1973	1963–1970	4000–5000	6/6	20 mo–8 y
Arthur,[1] Queen Elizabeth, 1977	1957–1970	3000–5000	22/23	3 mo–15 y
Gibbin and Henk,[17] University Hospital of Wales, 1978	1957–1976	4250–5500	12/14	Mean 8.7 y
Wang et al.,[49] University of Iowa, 1988	1950–1981	2900–6750	12/15	5–35 y
Thomsen et al.,[45] Aarhus, Denmark, 1975	1959–1973	5000–6000	13/15	Few months to 11 y
Reddy et al.,[36] University of Kansas, 1983	1958–1979	2200–5600	11/11	2–22 y
TOTAL			349/384 (91%)	

(Modified from Springate SC, Weichselbaum RR. Radiation or surgery for chemodectoma of the temporol bone: a review of local control and complications. Head Neck 1990;12:304)

TABLE 30-5. Glomus Tympanicum and Jugulare Chemodectomas: Local Control With Surgery Alone

Institution	Dates	Local Control/Treated	Follow-Up
Rosenwasser,[37] Mount Sinai, 1969	1945–1966	14/20	1–25 y; mean 7.4 y
Spector and Sobol,[43] Washington University, 1980	1946–1979	57/68	Mean 6.2 y
Newman,[34] University of California (San Francisco), 1973	1952–1969	3/14	18 mo–7 y
Jackson,[24] Vanderbilt, 1982	1978–1982	87/89	2 mo–12 y
Brown,[3] Calgary, 1985	1953–1973	158+/174*	10 y
Cece,[5] Mount Sinai, 1987	1975–1985	16/17	Not stated
Thomsen,[45] Aarhus, Denmark, 1975	1959–1973	4/6	Few months to 11 y
Kim,[26] University of Virginia, 1980	1932–1978	10/17	1/30 y
TOTAL		349/405 (86%)	

* Because 16/231 patients had recurrences, and 174 were treated with surgery alone, the local control in the surgery alone group was at least 158/174.
(Springate SC, Weichselbaum RR. Radiation or surgery for chemodectoma of the temporal bone: a review of local control and complications. Head Neck 1990;12:304)

recurrence. Operative mortality is significant in some series.[51]

Only limited data are available for radiation therapy, but successes are reported for advanced disease. Valdagni and Amichetti[47] reported the radiation therapy results for 13 carotid body tumors occurring in seven patients treated between 1968 and 1987. Ten tumors were treated with radiotherapy alone, nine having no prior treatment and one being recurrent after previous surgery. Three patients had incomplete surgery followed by radiotherapy. After surgery, one patient had 3 × 3 cm residual gross disease and another patient had bilateral incompletely resected chemodectomas, one with midjugular lymph node metastases. Doses were in the range of 4600 to 6000 cGy. There were three complete responses, seven partial responses, and three without change. Local control or stabilization was obtained in all patients with a follow-up ranging from 1 to 19 years. No acute or long-term toxicity was recorded. Guedea and coworkers[19] reviewed the University of Florida experience for five patients with carotid body tumors treated by radiotherapy between 1980 and 1986. Tumors were bilateral in two cases. Three lesions had previously been treated with surgery, and four patients had had no prior treatment. Complete regression occurred in two lesions, partial regression in two, and no change in two. One patient was irradiated after two operations and a previous course of radiotherapy; the tumor progressed and the patient died of the disease.

FOLLOW-UP POLICY

Baseline CT or MRI may be useful for follow-up of temporal bone tumors. The relative merits of each study for follow-up were discussed in the diagnostic imaging section of this chapter. Repeat angiograms may be ordered if recurrence is suggested by the imaging studies. Although late recurrences are often predicted after treatment with irradiation, they are seldom observed. It is not unusual to have a persistent blue–red mass behind the eardrum after irradiation, even though the patient is clinically improved and there is no evidence of progression. Five percent to 10% of all patients develop a second chemodectoma, often in the head and neck area; about one third to one half of the patients with a familial history may have multiple glomus tumors.

COMPLICATIONS OF TREATMENT

Surgery

Temporal Bone Tumors

GLOMUS JUGULARE

> If total extirpation of the tumor is the goal of surgery, then a high rate of postoperative complications is to be expected.
>
> *Cece and associates*[5]

Cece and associates[5] reviewed the postoperative complications in the management of 17 large glomus jugulare tumors treated between 1975 and 1985. All 17 patients suffered either new cranial nerve deficits or exacerbation of preexisting palsies. Aspiration and dysphagia were troublesome in 13 patients postoperatively. Cerebrospinal fluid (CSF) leak, meningitis, and wound infection also occurred. The incidence of postoperative complications is outlined in Table 30-6.

Poe and coworkers[35] reported the results of a survey (by telephone or mail) of 59 patients who had surgery for glomus jugulare tumors between 1970 and 1987 (2 to 19 years of follow-up). Sixty-two other patients were lost to follow-up. Four patients (3%) suffered fatal postoperative complications. In addition to these fatalities, Poe and associates (and others) have previously reported life-threatening complications including strokes, CSF leaks, arrhythmias, wound infections, and meningitis. Intentional sacrifice of cranial nerves IX and X (50%) or VII, XI, and XII (35% to 40%) was common, resulting in aspiration (41%), hoarseness (47%), dysphagia (40%), facial paralysis (36%), dry eye (38%), temporomandibular joint

TABLE 30-6. Incidence of Postoperative Complications

Complication	Patients
New cranial nerve palsy or exacerbation of preoperative palsy	17
Aspiration and dysphagia of new onset	10
Cerebrospinal fluid leak	2
Wound infection	1
Meningitis	1
Chronic otorrhea with nonhealing mastoid cavity	1
TOTAL	32 complications in 17 patients

(Cece JA, Lawson W, Biller HF, Eden AR, Parisier SC. In the management of large glomus jugulare tumors. Laryngoscope 1987;97:154)

dysfunction (17%), mandibular malocclusion (24%), shoulder weakness (50%), shoulder pain (33%), oral disability (due to loss of cranial nerve XII) (16%), gustatory tearing (17%), and altered taste (53%). Poe and colleagues[35] stated that most patients learned to compensate for the deficits by performing a variety of maneuvers such as turning the head sharply to the side while swallowing, consuming special soft diets, and using ocular lubricants, or had a variety of reconstructive procedures including Teflon vocal cord injections once (40%) or on multiple occasions (7%), laryngeal reinnervation or reconstruction (5%), tarsorrhaphies or gold weight eyelid implants (percentage not stated), and temporomandibular joint surgery (3%).

Jackson and associates[24] reported the postoperative complications for 67 patients treated for glomus jugulare tumors. The operative mortality was 5%, with an average hospital stay of 23 days. The facial nerve was transposed in 33 of 67 patients and reestablished by primary nerve reapproximation in 6 patients and cable graph in 11 patients. CSF leak occurred in 11%, and wound infection and meningitis occurred in 6%. Aspiration occurred in 23% of cases. There were two known recurrences.

In a series of 155 glomus temporale tumors, Fisch and Mattox[13] reported only one postoperative death. Morbidity for class C tumors, however, included complete conductive hearing loss, frequent cranial nerve palsies, and CSF leak.

Similar examples of complications for glomus jugulare operations were reported in several other series.[10,16,43] Dysphagia and aspiration are the most debilitating problems after paralysis of nerves IX, X, and XII. Prolonged nasogastric tube feeding may be required for aspiration pneumonia. Cricopharyngeal myotomy and augmentation of the paralyzed vocal cord with Teflon are useful to minimize these problems. Delayed death due to aspiration is reported. A gold-weight implant of the upper eyelid is used for nerve injury of cranial nerve VII.

During the removal of skull base lesions, arterial spasm may be encountered, and appears more frequently in younger patients. Stroke and possible death are potential major side effects of this complication.[41]

These problems make one wonder if many patients are more debilitated by their treatment than by their tumor.

GLOMUS TYMPANICUM. Jackson and associates[25] reported no complications for 53 patients.

Glomus Vagale

Jackson and coworkers[25] reported the complications of surgery in 14 patients with glomus vagale tumors. The facial nerve was transposed in four, reapproximated in one, and cable grafted in one. The operative mortality was 7%. Prophylactic tracheostomy and gastrointestinal decompression have reduced the problem of aspiration in recent years.

Biller and associates[2] reviewed the postoperative complications for 18 patients treated between 1972 and 1988. It was necessary to resect a normal vagus nerve in 12 patients and a normal hypoglossal nerve in 8. It was necessary to resect the invaded internal carotid artery in three cases, and it was inadvertently injured in another case. There was a single postoperative death; one patient had bilateral palsy of cranial nerve X and died 2 years after surgery as a result of acute airway obstruction.

Radiation Therapy

There have been isolated reports of brain necrosis; these cases were associated with high doses, high daily fractions, or repeat courses of irradiation. This complication should not occur at a dose of 4500 cGy given at 180 cGy per day, 5 days a week. Other complications include cholesteatoma and sequestrum of the mastoid, and serous otitis. Detectable damage to the hearing mechanism and vestibular apparatus has not been reported to occur with doses of 4500 to 5000 cGy to the normal temporal bone. Cranial nerve palsy due to irradiation should not occur. The complication rate is greater when both operation and irradiation are used.[8]

Konefal and associates[27] reported a single complication of radiotherapy in 26 patients. This patient developed an osteoradionecrosis in the tympanic bone after a tumor dose of 5418 cGy using a mixed beam treatment.

Harwood and coworkers[21] reported an instance of brain necrosis when a double dose was given inadvertently as the result of a technical error.

Combined Therapy

The complications of combined operation and irradiation are essentially the complications listed under surgery.

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31

CARCINOMA OF THE THYROID

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Thyroid carcinoma represents a spectrum of diseases with markedly different clinical behaviors. Opinions vary considerably regarding the means of establishing the diagnosis, the extent of initial surgery, and the role of various surgical adjuvant treatments. Because a number of factors influence the course of disease, treatment must be individualized. The majority of patients are adequately managed with operation plus thyroid hormone replacement, with or without radioiodine. Most patients do not require external-beam radiotherapy, but there are certain subgroups in whom it is indicated and beneficial.

EPIDEMIOLOGY

Thyroid carcinoma is a relatively rare disease. In 1993, the American Cancer Society predicted 12,700 new cases (9,300 women, 3,400 men) and 1,050 deaths (600 women, 450 men) in the United States.[16] The prevalence seems to be fairly uniform throughout the world wherever adequate statistics are available.[38] In the United States, there is a higher incidence of thyroid cancer in whites than blacks.[37]

The disease occurs primarily in young and middle-aged adults.[160] Only about 5% of all cases occur before 15 to 20 years of age. The peak incidence of papillary carcinoma occurs 15 to 20 years earlier than that of follicular carcinoma, which is about 10 years before that of anaplastic carcinoma.[63,160] At the M.D. Anderson Hospital, only 8% of patients with anaplastic carcinoma were under 50 years of age.[1]

Although most medullary carcinomas (approximately 80%) occur sporadically, they may also occur as a component of two complex endocrine syndromes, multiple endocrine neoplasia type IIA (MEN IIA) or type IIB (MEN IIB). The peak incidence of sporadic disease is in the sixth decade versus the second or third decade for familial disease.[26,156] All types of medullary carcinoma produce elevated plasma calcitonin levels.

MEN IIA is inherited as an autosomal dominant trait and is often associated with pheochromocytoma (10%) and parathyroid adenoma or hyperplasia (60%).[48] The variant syndrome, MEN IIB (medullary thyroid carcinoma, mucosal neuromas, pheochromocytoma, and a marfanoid habitus), is usually sporadic, but familial cases have also been reported.[97,156]

For both papillary and follicular carcinomas, the female-to-male ratio is 2.5 to 3.0 : 1.[30,160] The sex ratio for anaplastic and medullary carcinomas is approximately equal.[1,30,87,160]

ETIOLOGY

Exposure to ionizing radiation is the only well-documented etiologic factor associated with thyroid carcinoma. It is estimated that 1 to 2 million children received low-dose irradiation for benign conditions during the 1940s and 1950s in the United States, and that as many as 7% might eventually develop thyroid cancer.[88] Most radiation-induced cancers are well differentiated. The usual latent interval is 10 to 30 years, but cases outside both time limits have been observed (see Chap. 13). In many series reported in the 1970s and early 1980s, approximately 10% to 20% of patients treated for thyroid cancer gave a history of head and neck or chest irradiation. For the past 25 years, irradiation has seldom been given to young patients with benign disease, and the number of cases secondary to irradiation appears to be declining.[88]

Although it has been suggested that some tumors are hormone-dependent, there is no strong evidence to indicate that human thyroid cancer develops in response to elevated levels of thyrotropin (thyroid-stimulating hor-

mone; TSH), as has been shown in animals. Attempts to link the geographic distribution of nodular goiter to that of thyroid cancer have yielded inconclusive findings.

ANATOMY

Although the majority of anatomic variations in the region of the thyroid gland are minor, they occur frequently and are therefore of considerable importance to the surgeon. Too great reliance must not be placed on the "normal" anatomy if one is to avoid major surgical complications, primarily recurrent laryngeal nerve palsy or hypoparathyroidism.

The thyroid gland is situated anteriorly in the low neck in close proximity to the larynx, trachea, esophagus, parathyroid glands, recurrent laryngeal nerves, cervical sympathetic chain, and carotid sheath and its contents (Fig. 31-1).[44] The lateral lobes are approximately 5 cm in length and extend to the level of the mid-thyroid cartilage superiorly and to the sixth tracheal ring inferiorly; the lobes are connected in the midline by the isthmus at the level of the second to fourth tracheal rings (Fig. 31-2).[93] The isthmus is occasionally absent.[154] A pyramidal lobe is present in 40% to 50% of patients[40,67] and ascends for a variable distance toward the hyoid bone, usually slightly to the left of midline.

The functional unit of the thyroid gland is the follicle, which consists of a single layer of cuboidal epithelium surrounding a colloid-space. The follicles are separated from each other by a highly vascular connective tissue in which are situated the parafollicular cells, which secrete calcitonin. Connective tissue fibers from the capsule penetrate the gland, separating groups of follicles into lobules.

The thyroid gland develops as a tubular evagination from the base of the tongue. It grows downward in front of the thyroid cartilage and trachea to reach the position it will occupy in adult life. The distal end of the structure proliferates to form the thyroid gland, whereas the remainder usually undergoes obliterative fibrosis to form a solid cord whose pharyngeal aspect is marked by the foramen cecum of the tongue. The tongue and hyoid bone, which form in the embryo later than the thyroglossal duct, often invest a segment of the duct in their developmental process. The duct is frequently seen to pass through the midportion of the hyoid bone. The infrahyoid portion of the duct remains in the midline where it passes anteriorly to the thyroid cartilage. Persistence of the vestigial tubular structure may result in later development of thyroglossal duct cyst or multiple cysts along the course of the tract in the anterior midline of the neck. The cyst wall may contain nests of thyroid follicles, which, on rare occasions, give rise to thyroid carcinoma.[69,76,143]

The capsule of the gland is formed rather late in fetal life from adjacent mesenchymal tissue; consequently, tissues foreign to the thyroid gland, such as the parathyroid glands, are often enclosed within it.[40] Although the recurrent laryngeal nerve is also said to pierce the capsule occasionally and enter the substance of the gland, such an occurrence must be rare and was never observed by Martin or his colleagues[80] over a 30-year period at Memorial Sloan-Kettering Hospital in the performance of up to 225 thyroid operations per year.

The right recurrent laryngeal nerve recurs around the right subclavian artery, and the left recurs around the aortic arch. In the region of the thyroid gland, the nerves usually lie in a protected position in the tracheoesophageal grooves, although, in some cases, they may be lat-

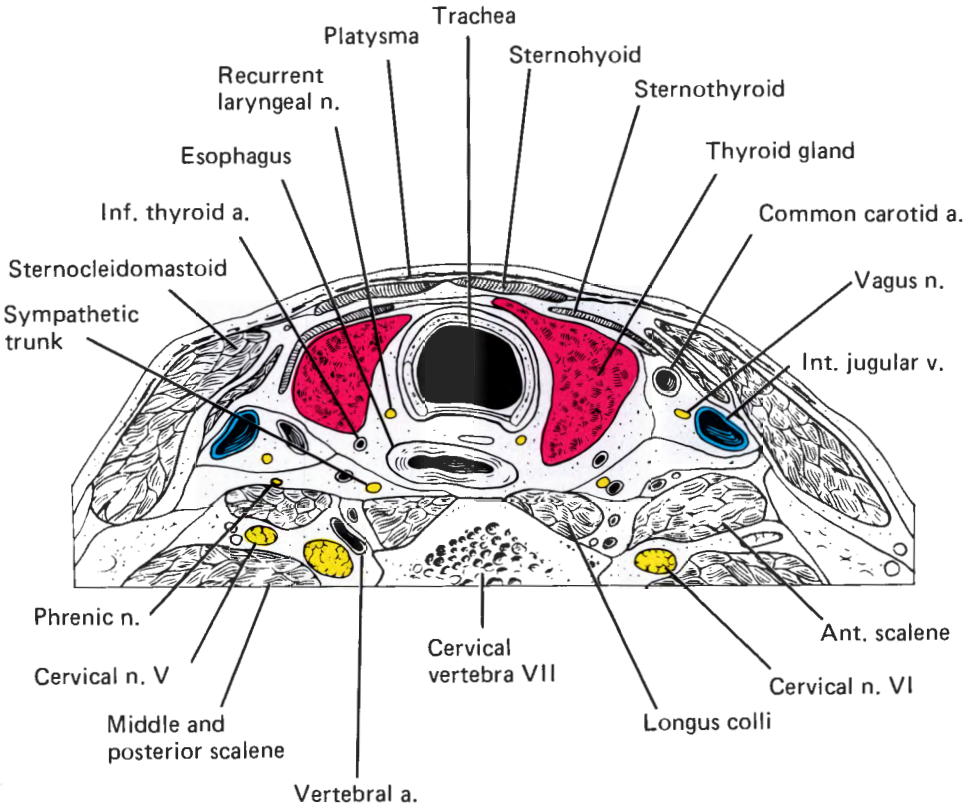

Figure 31-1. Cross section of the neck through the C7 level. (Redrawn from Eycleshymer AC, Schoemaker DM: A cross-section anatomy. New York, D. Appleton-Century, 1938:55)

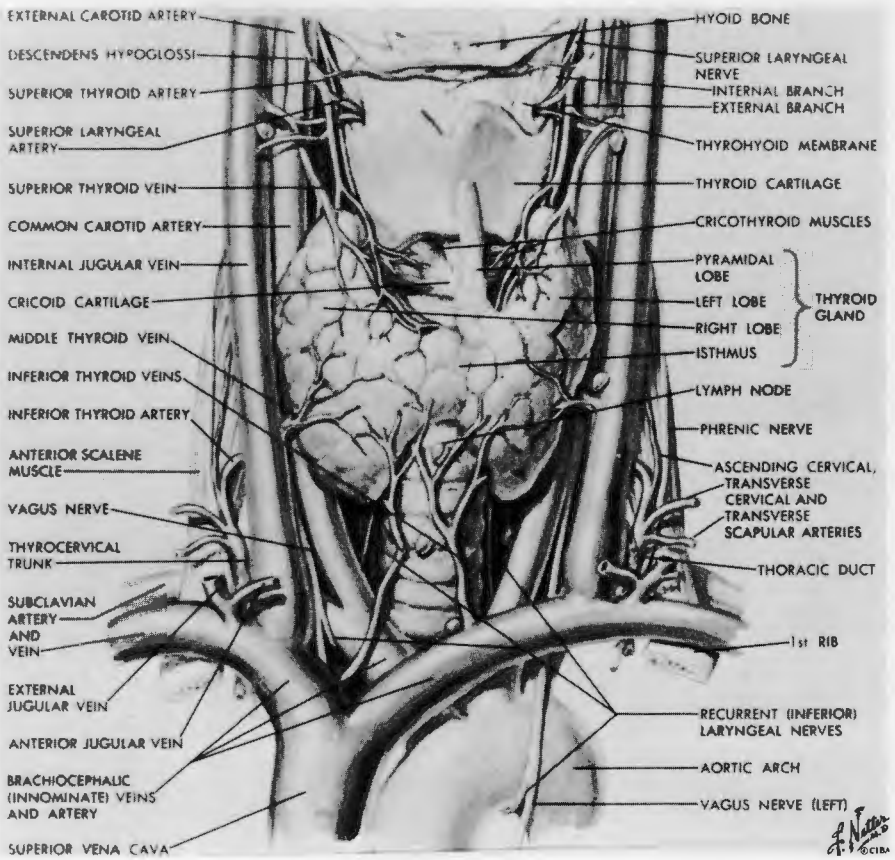

Figure 31-2. Regional anatomy of the thyroid gland. (CIBA Pharmaceutical Company, Division of CIBA-Geigy Corporation. Reprinted with permission from the CIBA Collection of Medical Illustrations, illustrated by Frank H. Netter, MD. All rights reserved. Plate 2, p 42)

eral or, more rarely, anterolateral to the trachea.[67] Before it enters the larynx under cover of the inferior constrictor muscle behind the articulation of the inferior cornu of the thyroid cartilage with the cricoid cartilage, the nerve is intimately related to the medial surface of the thyroid gland. The inferior thyroid artery is a useful guide to the location of the recurrent laryngeal nerve;[40] the nerve may pass in front of or behind the artery or through its branches. The recurrent laryngeal nerve may branch well below the larynx.[30,80,95] Simply visualizing the nerve in the tracheoesophageal groove is no insurance that it will not be injured higher up. The most frequent site of recurrent laryngeal nerve injury is under the upper pole of the gland,[80,95] where the nerve is frequently embedded in the fascial attachment (adherent zone, ligament of Berry) of the thyroid gland to the cricoid cartilage and upper tracheal rings and where more than one branch of the nerve may be present.[30,67,80,154] The nerve may also be injured during ligation of the inferior thyroid artery.

If the right recurrent laryngeal nerve cannot be located at operation, the possibility of a nonrecurrent nerve should be entertained. This variation, associated with an anomaly of the aortic arch and its branches, is probably present in less than 1% of patients, but will be seen by any surgeon who performs a large number of thyroid operations.[40,67,80,95,100] Instead of looping under the subclavian artery, a nonrecurrent nerve may originate from the cervical trunk of the vagus at the level of the cricoid or thyroid cartilage and pass horizontally to the larynx, or it may first descend for several centimeters and then ascend in essentially the position of a normal recurrent laryngeal nerve.[100] We have not seen reports of the anomaly on the left side.

The normal parathyroid glands vary in size, number, and position and are not easily identified at surgery.[30,80] Their color, texture, and relationship to the branches of the inferior thyroid artery may help distinguish the glands from lymph nodes, fat, or thyroid tissue.[40] Typically, the glands are 6 mm long, 3 to 4 mm wide, and 1 to 2 mm thick; sometimes, in the region of the normal glands, there may only be many minute islands of parathyroid tissue scattered in the connective tissue and fat.[154]

Generally, there are two superior and two inferior glands. The upper glands are relatively constant in position; they are usually adherent to the capsule of the thyroid gland at the junction of its upper and middle thirds (at approximately the level of the upper portion of the cricoid cartilage). Embryonically, the lower parathyroid glands develop cephalad to the superior glands, in close association with the thymus; they are drawn below the superior glands when the thymus migrates caudad. The parathyroid glands normally descend only as far as the lower pole of each thyroid lobe. However, because of their "embryologic motility,"[40] the inferior glands are more variable in position than the superior ones. They may be found within the substance of the thyroid gland, or they may migrate with the thymus into the chest; if they fail to migrate, they remain above the superior parathyroids, near the bifurcation of the common carotid artery.

The upper parathyroid glands are generally cephalad to the inferior thyroid artery and its uppermost

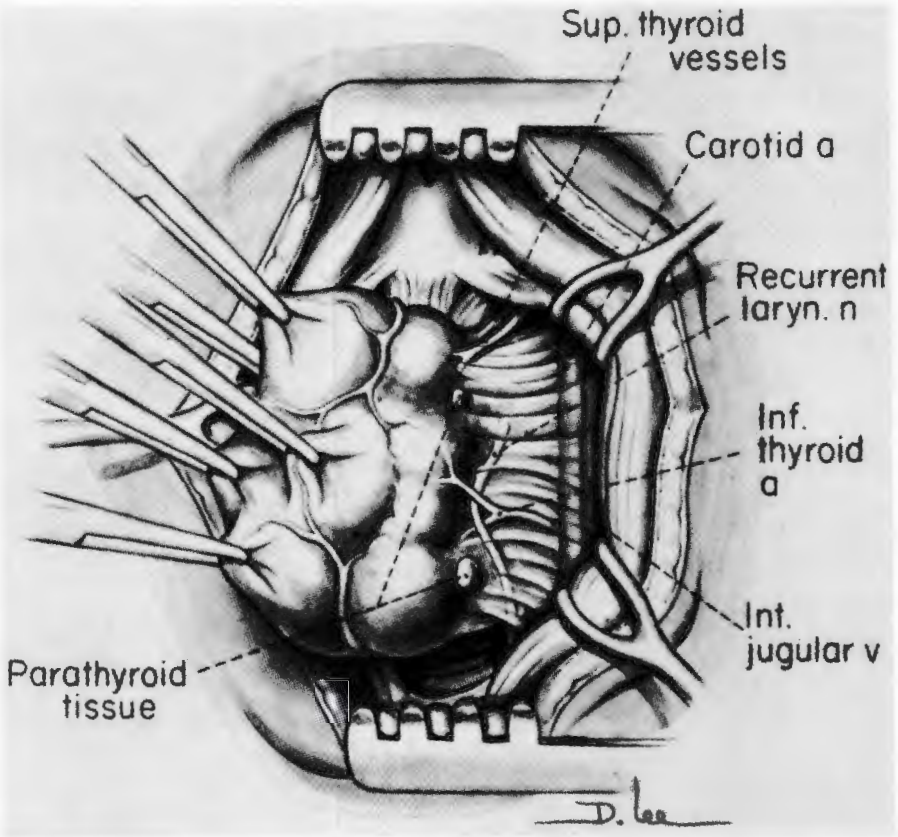

Figure 31-3. Idealized diagram showing relationship of inferior thyroid artery to recurrent laryngeal nerves and parathyroid glands. (Dozois RR, Beahrs OH. Surgical anatomy and technique of thyroid and parathyroid surgery. Surg Clin North Am 1977;57:658)

branches, whereas the lower glands are caudad to the lowermost branches (Fig. 31-3). When the glands are hard to find, it may be of some help to trace the arterial branches.[40]

Lymphatic capillaries are arranged around the thyroid follicles and drain into a lymph network in the capsular region of the gland. From there, collecting trunks drain to a number of nodal sites, including those of the internal jugular chain, the Delphian node (one or two nodes overlying the cricothyroid membrane, present in about one half of patients), and the pretracheal and paratracheal nodes in the lower neck.[115] Spread of thyroid cancer into the mediastinum is generally limited to lymph nodes in the anterosuperior segment, behind the manubrium and cephalad to the innominate veins. Spread of cancer to this region is almost always associated with spread to lateral cervical lymph nodes. Drainage to more inferiorly located mediastinal nodes is rare in the absence of extensive anterosuperior mediastinal or pulmonary metastases.[15] McCormack and Sheline described seven thyroid cancer patients seen over a 20-year period at the University of California, San Francisco, in whom metastases occurred to parapharyngeal or retropharyngeal lymph nodes, as recognized by the occurrence of a submucosal mass in the pharynx.[86]

PATHOLOGY

Carcinomas of follicular cell origin are subdivided into papillary, follicular, and anaplastic carcinoma; those arising from parafollicular cells are called medullary (solid) carcinoma. The relative frequencies of thyroid carcinomas in 1181 patients treated at the Mayo Clinic over a 35-year period are shown in Table 31-1;[161] these proportions are similar to those seen in other large series.[126] Papillary and follicular lesions (often referred to as the well-differentiated thyroid carcinomas) accounted for 80% of the total group. The percentage of patients with anaplastic carcinoma was higher at the Mayo Clinic than in some other large series; only 7% of 1174 thyroid carcinomas seen at the M.D. Anderson Hospital were true anaplastic lesions.[1]

The majority of papillary carcinomas contain both papillary and follicular elements in varying proportions; whether the lesion contains equal proportions of the two

TABLE 31-1. Classification of Thyroid Carcinoma

Histology	Patients	Percentage
Papillary carcinoma	736	62.3
Follicular carcinoma	208	17.6
Slight or equivocal invasion	104	
Moderate to marked invasion	104	
Medullary (solid) carcinoma	77	6.5
Anaplastic carcinoma	160	13.6
TOTAL	1181	100.0

Note: Mayo Clinic data; patients treated between 1926 and 1960. (Adapted from Woolner LB, Beahrs OH, Black BM, McConahey WM, Keating FR Jr. Thyroid carcinoma: general considerations and follow-up data on 1181 cases. In: Young S, Inman DR, eds. Thyroid neoplasia. New York, Academic Press, 1968:54, 63)

patterns or is mostly papillary or mostly follicular does not affect its biologic behavior. Considerable microscopic variation may occur from one portion of the tumor to another, and a primary tumor that is chiefly papillary may be associated with metastatic nodes that have largely a follicular architecture.[48] Microscopic diagnosis is not difficult in the majority of cases. The lesions are typically unencapsulated, have a high incidence of multifocality within the gland (whether these multifocal lesions represent true multicentric foci of origin or intrathyroidal lymphatic dissemination is not known),[30] and have almost no tendency toward vascular invasion. Psammoma bodies are frequently present.[160] Metastases generally contain both papillary and follicular elements.

Follicular carcinomas tend toward gross encapsulation. Papillary structure is, by definition, absent. Two morphologic subtypes are recognized, depending on invasiveness. The diagnosis of a carcinoma with slight or equivocal invasion is made on the basis of vascular invasion in the capsular region.[60] Often, the pathologist must examine multiple histologic sections from this region to distinguish a well-encapsulated follicular carcinoma from an adenoma. Follicular carcinomas with moderate to marked invasion are generally of a higher grade than less invasive lesions and often demonstrate obvious invasion of thyroid parenchyma.[60]

Hürthle cell carcinoma is considered by many to be a variant of follicular carcinoma. Most Hürthle cell lesions are histologically benign. In many instances, the malignant potential is difficult to judge histologically, and occasional metastases from benign-appearing tumors have been reported. Tumor size, per se, is not a reliable predictor of malignant potential. Failure of Hürthle cell tumors to take up radioiodine further distinguishes them from follicular carcinoma.[2]

Anaplastic has often been used as a wastebasket classification into which some investigators have placed spindle and giant cell carcinomas, squamous cell carcinoma, occasional sarcomas, small cell carcinomas, and perhaps some lymphomas. Accurate diagnosis is important so that appropriate therapy may be planned. Many so-called small-cell anaplastic carcinomas are probably lymphomas.[1,158] Histopathology may not allow one to distinguish between the two, and electron microscopy and cell surface markers specific for lymphoid tissue are necessary. Clinicopathologic correlation is important.

The M.D. Anderson Hospital group regards spindle and giant cell carcinomas as the only anaplastic neoplasms of thyroid epithelial origin and provides evidence that these lesions develop from preexisting differentiated carcinomas. Eighteen (21%) of 84 patients had a history of differentiated carcinoma; histology sections from 66 patients (78%) revealed coexisting differentiated and anaplastic carcinoma, frequently with areas of transition from one pattern to the other.[1]

Medullary thyroid carcinoma is the only thyroid cancer that contains an amyloidlike substance. Although a frequent finding, this material need not be present to establish the diagnosis. Both the primary lesion and the metastases usually contain the substance.[60] Histologically, sporadic medullary thyroid carcinoma appears no different from that occurring in patients with the MEN II syndromes. However, in MEN IIA or MEN IIB, the cancer is virtually always bilateral within the gland. The sporadic form may be either unilateral or bilateral, more commonly the former.[62,157]

PATTERNS OF SPREAD

Each histologic type of thyroid carcinoma possesses its own distinctive natural history.

Papillary carcinomas are characterized by slow growth. Extension of the primary tumor through the capsule of the gland into the soft tissues of the neck with invasion of surrounding viscera is unusual (5% to 15%) at presentation;[7,46,83,85] most of the patients in whom such extension occurred in the Mayo Clinic series were over 40 years of age at diagnosis.[160] Seven percent of previously untreated patients at Memorial Sloan-Kettering Hospital, New York City, had grossly unresectable disease secondary to invasion of the great vessels, larynx, trachea, or pharynx.[46] The larynx may be directly invaded, or tumor may extend around the posterior border of the thyroid cartilage to involve the pyriform sinus and paraglottic fat space. Hemorrhage from intraluminal tumor may occur. The esophagus, trachea, and recurrent laryngeal nerves can be invaded by direct extension or by metastatically involved paratracheal lymph nodes in the tracheoesophageal groove.[84]

Forty percent to 50% of patients with papillary carcinoma have gross evidence of regional lymph node metastases at operation;[60,83,85,160] in patients under 15 years of age, the incidence approaches 90%.[49,58] The true incidence of lymphatic metastases at presentation is higher than 50% because at least half of the patients with grossly normal lymph nodes are found to have metastases if they are systematically sampled.[46,80,83,96] The earliest metastases are generally to neck nodes ipsilateral to the primary lesion. Mediastinal metastases usually occur later; mediastinal metastases large enough to be detected on a chest roentgenogram were noted in 4 of 265 previously untreated patients at Memorial Sloan-Kettering Hospital.[46] Involved lymph nodes tend to remain discrete and mobile, without extension of tumor through the capsule.[58,133] Distant metastasis at presentation is unusual (3% of previously untreated patients at Memorial Sloan-Kettering Hospital)[21,46] and encountered mainly in patients with extracapsular extension;[108] less than 10% of patients developed distant metastases (usually to the lung) at some time during the course of their disease.[56,83,160]

Follicular carcinomas, like papillary lesions, are characterized by slow growth. As with papillary carcinoma, locally advanced, unresectable primary disease is unusual at presentation.[21,161] Lymph node metastases are seldom seen, except in the presence of extensive capsular invasion, recurrent tumor,[159] or extraglandular extension.[21] Twelve (7%) of 178 patients with follicular carcinomas had evidence of distant metastases, usually to the lung or bone, on referral to the Lahey Clinic;[21] if one assumes that virtually all of these metastases occurred in patients with moderate to marked capsular and vascular invasion, one might expect metastases at presentation in 15% to 20% of this group.[7] Distant metastasis after treatment is a frequent problem in patients with highly invasive lesions.[160]

Hürthle cell neoplasms spread to regional lymph nodes, bone, and lung.

Anaplastic carcinomas are among the most aggressive of human tumors. In 84 cases seen at M.D. Anderson Hospital over a 28-year period, only three patients had limited disease confined to the gland without evidence of distant metastases.[1] The primary lesions tend to be large and fixed, with invasion of adjacent structures. Skin in-

vasion and fixation are not rare, giving rise to dermal lymphatic metastases on the chest and abdominal walls. Neck nodes are usually involved, although sometimes the primary tumor is so extensive that regional node status is difficult to assess. Axillary nodes are involved in some instances. In contradistinction to the mobile lymph nodes of differentiated lesions, those of anaplastic carcinoma are often fixed. Almost half (41 of 84) of the M.D. Anderson Hospital patients had distant metastases on admission.[1]

Medullary carcinoma is bilateral in virtually all familial cases, and it may be unilateral (80%) or bilateral (20%) in sporadic cases. At presentation, 25% of patients have palpable lymph nodes; 50% to 75% of all patients have positive lymph nodes at thyroidectomy. Involvement of mediastinal lymph nodes is frequent. Distant metastases occur most often in the liver, lungs, and bones.

CLINICAL PICTURE

Because the thyroid is an endocrine organ, one might expect to find malignant tumors that produce excessive quantities of thyroid hormone, but such a situation is rare.[142]

Differentiated carcinoma commonly presents as an asymptomatic unilateral mass that is either found incidentally on a routine examination or is noted by the patient. In many instances, some abnormality of the gland has been known to be present for several years before diagnosis.[38] Although rapid enlargement may suggest malignancy, such enlargement may also occur secondary to hemorrhage into an adenoma or cyst. Pain and tenderness suggest thyroiditis.[7,30] Lymphadenopathy may occur in Hashimoto's thyroiditis as well as in malignant conditions.[30]

In 149 (21%) of 704 Mayo Clinic patients with papillary carcinoma, the primary tumor was a clinically unsuspected, small (1.5 cm) lesion that produced no lymph node metastases and was incidentally found when operation was performed for a goiter or some other benign problem.[152,161]

Another relatively common presentation (95 of 704 patients or 13% at the Mayo Clinic and approximately 15% at Memorial Sloan-Kettering Hospital) of papillary carcinoma is with regional lymph node metastases (usually multiple nodes, sometimes massive) from a clinically inapparent, small primary cancer.[46,98,161] In the past, these metastases were said to represent lateral aberrant thyroid tissue; true aberrant thyroid tissue of embryonic origin occurs in the midline, along the path of the thyroglossal duct. This so-called unknown primary presentation is most commonly seen in young patients.[7] A mid or lower jugular lymph node is the site of involvement in approximately two thirds to three quarters of the patients.[99] In cases of unilateral lymph node metastases, the primary lesion is generally found in the ipsilateral lobe.[46,80] The primary cancer is often too small to produce a cold nodule on radioiodine scan.[77] A cold nodule was present in 60% of patients in the series of Park and Min.[99]

Fewer than 100 cases of thyroid carcinoma have been reported to arise from thyroglossal duct cysts. There was associated papillary carcinoma in the thyroid gland in approximately 25% of patients in whom the gland was removed.[69,76,143] Women are affected slightly more often than men (1.5 to 1.0). Most tumors are papillary in histology. Medullary carcinomas do not occur in thyroglossal duct cysts, because they arise from parafollicular cells, which are embryologically unrelated to the outpouching from the tongue base. The tumors usually arise just anterior to the hyoid bone or thyrohyoid membrane. Fixation to the hyoid bone is common. The tumor is most often associated with a cyst. Although there is no definite way to diagnose carcinoma in the cyst or tract remnant preoperatively, the presence of malignancy may be inferred from imaging findings. Thyroglossal duct cysts are usually unilocular or multilocular with relatively minor solid components. If the thyroglossal tract mass is predominantly solid on computed tomography (CT) or magnetic resonance imaging (MRI), cancer should be suspected. Distant metastases are rare.

Even rarer than carcinoma of the thyroglossal duct cyst is carcinoma of the lingual thyroid. Greater than 90% are papillary carcinomas. Symptoms include intraoral mass, dysphagia, dysphonia, and dyspnea.[129]

Occasionally, a pathologic bone fracture is the presenting symptom of follicular carcinoma.[30,121]

Primary anaplastic carcinomas are typically large, hard, and fixed and grow rapidly. Local symptoms due to compression or invasion of the esophagus, airway, or recurrent laryngeal nerves are often marked and may overshadow symptoms of distant metastases, which also occur frequently. Symptoms include pain, a sensation of tightness, dysphagia, dyspnea, stridor, and hoarseness. When the clinical picture fits that of anaplastic carcinoma, diagnosis by fine-needle aspiration is recommended to avoid treatment delay and the problem of tumor growing through an incisional biopsy site.

At presentation, most patients with medullary carcinoma are asymptomatic and are referred for evaluation of a painless thyroid mass.[26,62] Ten percent have symptoms due to extensive local invasion (pain, dysphagia, or hoarseness), and their tumor is locally unresectable in a substantial number of cases.[62] Twenty to 30% of patients have significant diarrhea at presentation, most commonly when extensive regional or distant metastases are present.[62,134] The mechanism is unknown, but it is probably due to elaboration of a hormone by the tumor. Diarrhea frequently precedes the diagnosis of cancer by months to years and occasionally is the only complaint at presentation.

Almost all patients with medullary thyroid carcinomas large enough to be palpated have elevated basal plasma thyrocalcitonin levels. Even in the presence of markedly elevated levels, hypocalcemia is almost never seen in medullary carcinoma; in fact, hypercalcemia is more common and occurs in patients with MEN IIA. Hyperparathyroidism occurs in approximately 60% of MEN IIA patients; it is detected by an elevated blood calcium concentration and confirmed by serum parathormone levels.[157]

In patients with MEN IIA or MEN IIB, to avoid a possible hypertensive crisis, it is essential to exclude the presence of, or treat, a pheochromocytoma before any neck operation is performed.[97,156] The pheochromocytomas associated with medullary carcinoma usually occur in the second or third decade, are bilateral in approximately 70% of cases, and almost always are confined to the adrenal gland.[26,157] Elaboration of adrenocorticotropic hormone (ACTH), histaminase, prostaglandins, and serotonin has been reported in patients with medullary carcinoma and may produce a variety of symptoms.

MEN IIB patients are characterized by typical facies (ie, puffy lips, soft tissue prognathism, broad base of the nose, and everted eyelids), multiple mucosal neuromas, marfanoid habitus, and a variety of skeletal abnormalities.[97]

METHODS OF DIAGNOSIS

A thyroid nodule can be palpated in 3% to 4% of the U.S. population;[4,70,108,139] the incidence increases with age and is higher in women than men.[4] The frequency with which nodules are found at autopsy is higher than the clinical incidence.[90] Thyroid nodules (usually less than 1 cm in size) are incidentally detected in as many as 25% to 50% of patients who undergo imaging studies for other reasons. Because the prevalence of thyroid cancer is low compared with these figures, it is obvious that the majority of nodules are benign and, unless symptomatic, need not be resected. The problem for the thyroid surgeon is to separate out the small group of malignant lesions from the larger group of benign lesions.

At one extreme, the diagnosis of malignancy may be strongly suspected on clinical grounds alone, such as in a young patient with a history of head and neck irradiation who has a steadily enlarging, firm, solitary thyroid mass with or without lymphadenopathy. Similarly, a thyroid nodule in a child is highly suspect.[7] A patient with a family history of thyroid cancer or a patient with marked symptomatology suggestive of anaplastic carcinoma likewise generally presents little diagnostic challenge. Such patients generally require open exploration regardless of the findings of various laboratory tests.

At the other extreme, the clinical picture may be near-diagnostic of a benign condition, such as in an older patient with a relatively soft, multinodular goiter that has not changed for many years. Observation alone, perhaps with periodic ultrasound follow-up, may suffice unless there is some other reason (cosmesis or pressure symptoms) to remove the mass.

Between these two extremes, one finds many patients in whom the history and clinical findings are not so conclusive. Often the mass is unilateral, asymptomatic, and thought to be of recent origin. The differential diagnosis includes cysts, cancer, hyperplasia, adenomas, and some type of thyroiditis.

The goal of work-up is to avoid operation in those patients who do not need it. At the University of Florida, the main diagnostic tools are ultrasound and fine-needle aspiration. Radionuclide scans are usually not helpful; most nodules are "cold" whether benign or malignant. Many patients, however, have already undergone radionuclide imaging before referral to our institution. About 15% of palpable, apparently solitary nodules are shown to be functioning and therefore unlikely to be cancerous. These can be suppressed or followed by physical examination. Individual practices vary widely on the question of whether radionuclide studies are a cost-effective step in the algorithm for diagnosis and management of solitary nodules. The main utility of ultrasound is to determine whether the nodule is solitary or the gland is multinodular. Determination of whether the lesion is cystic or solid is of limited value because cancers can have hemorrhagic areas and appear partially and at times almost entirely cystic. Pure, simple cysts are extremely rare; complex cysts may harbor cancer, and biopsy should be performed. If the gland is multinodular and no nodule particularly stands out from the rest, aspiration and operation are usually not performed; the patient is observed. If there is one dominant nodule, it is aspirated and the cells are sent for cytology.

If the lesion is solitary and over 1.0 to 1.5 cm in size, the patient is likely to undergo operation whether it is cystic or solid. The nodule is, at minimum, aspirated, and if the cytology is malignant or suspicious or if the nodule does not disappear after aspiration, operation is usually indicated. If the cytology is benign and the lesion disappears, the patient is observed. Most elderly patients whose cytology is benign are observed. If the patient is young (20 to 30 years old) or in a high-risk group (history of neck irradiation in childhood, family history of multiple endocrine neoplasia syndrome, Hashimoto's thyroiditis, rapid tumor growth), the patient can bypass ultrasound and proceed directly to fine-needle aspiration or removal. False-positive and false-negative rates from fine-needle aspiration are generally reported to be 3% or less, with a low rate of complications.[45] Ultrasound can be used for the guidance of biopsy in selected cases.

The majority of patients are euthyroid. Elevated serum thyroglobulin occurs in a variety of thyroid diseases and has no diagnostic value.[145] Measurement of antithyroid antibodies is not helpful.[73] CT and MRI do not distinguish benign from malignant conditions if the mass is confined to the gland. Malignancy is suggested by extraglandular extension or lymph node metastasis. CT and MRI are most useful for showing extraglandular extension of tumor before surgery. These imaging studies provide an excellent map of the relationship of the normal and pathologic thyroid gland to surrounding structures in the low neck and thoracic inlet. All cervical and mediastinal nodal groups can be visualized by CT and MRI, including the tracheoesophageal groove, superior mediastinal, and retropharyngeal nodes, which cannot be evaluated by palpation or ultrasound. The normal CT and MRI anatomy of the low neck and thoracic inlet is shown in Figures 21-1 and 21-2.

Diagnostic MRI (CT if MRI is not available) should be done if clinical findings suggest thyroid carcinoma with capsular penetration. MRI is the preferred examination for evaluating esophageal or tracheal invasion because of its better contrast resolution and multiplanar capabilities. Ultrasound should precede MRI or CT if physical findings are indeterminate relative to the issue of extraglandular extension. Any carcinoma over 3 to 4 cm in size should be studied with MRI because of the likelihood of capsular penetration unless ultrasound *unequivocally* shows the mass to be completely surrounded by normal thyroid tissue.

The specific areas of interest and issues to be evaluated with MRI (or CT) include the following[79]:

Tracheal invasion. Axial and coronal sections should be done. The coronal sections should be 3 to 4 mm thick and parallel to the long axis of the trachea (Fig. 31-4).

Esophageal invasion. Axial T2-weighted and contrast-enhanced MRI images are required for the diagnosis of spread to the muscular wall of the esophagus (see Fig. 31-4).

Invasion of the laryngeal framework. Adjunctive CT may be necessary in selected cases.

Relationship of tumor to the carotid artery and course of the recurrent laryngeal nerve.

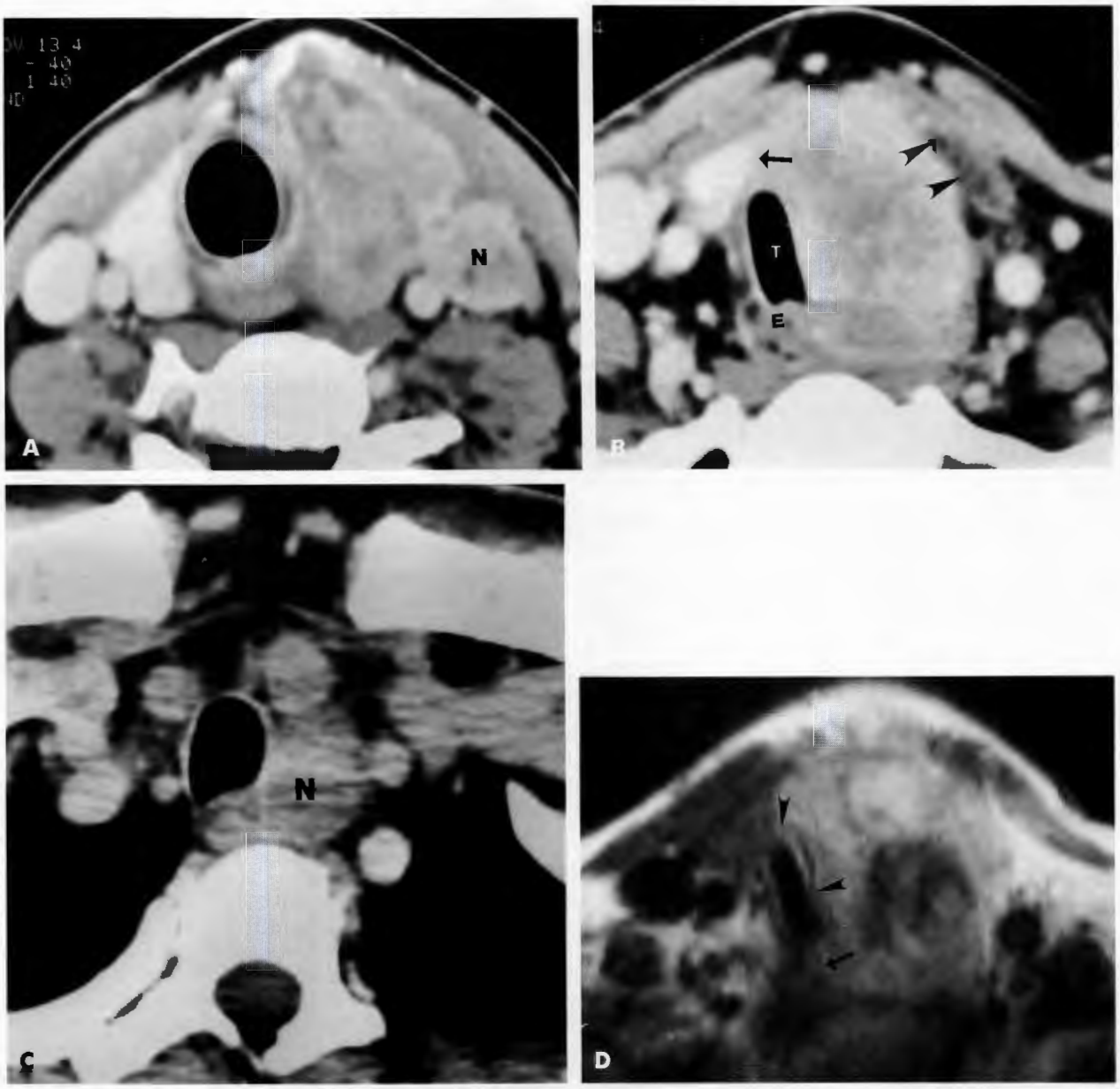

Figure 31-4. A 34-year-old man with medullary carcinoma of the thyroid gland. There was no history of MEN syndrome. (*A*) Contrast-enhanced CT shows a dominant thyroid mass and no definite extraglandular spread. A metastatic node (N) is present. (*B*) Contrast-enhanced CT about 2 cm inferior to that in *A*. Tumor extends across the isthmus to the opposite lobe (*arrow*). There is evidence of extraglandular spread laterally (*arrowheads*). The tumor compresses the trachea (T) and might invade the esophagus (E). (*C*) Contrast-enhanced CT about 2 cm below that in *B* shows a metastatic node (N) in the lower tracheoesophageal groove. (*D*) MRI shows probable fixation to the trachea at two points (*arrowheads*). MRI suggested esophageal wall invasion (*arrow*).

Evaluation of lymph nodes. MRI and CT are especially useful in demonstrating tracheoesophageal groove, superior mediastinal, and retropharyngeal adenopathy.

If open biopsy of a thyroid nodule is indicated, the recommended procedure is lobectomy. Lesser procedures (eg, "nodulectomy") are not advised because a diagnosis of cancer necessitates reoperation, which is technically more difficult and increases the risk of recurrent laryngeal nerve injury. At the time of operation, the gland is fully exposed to allow inspection and palpation of both lobes and adjacent structures. Should an enlarged lymph node or nodes be found, immediate frozen section may aid in planning the appropriate surgical procedure. Previously unrecognized contralateral thyroid nodules also influence the scope of the operation. Such surprises at surgery are largely avoidable if modern imaging studies are fully exploited (Fig. 31-5).

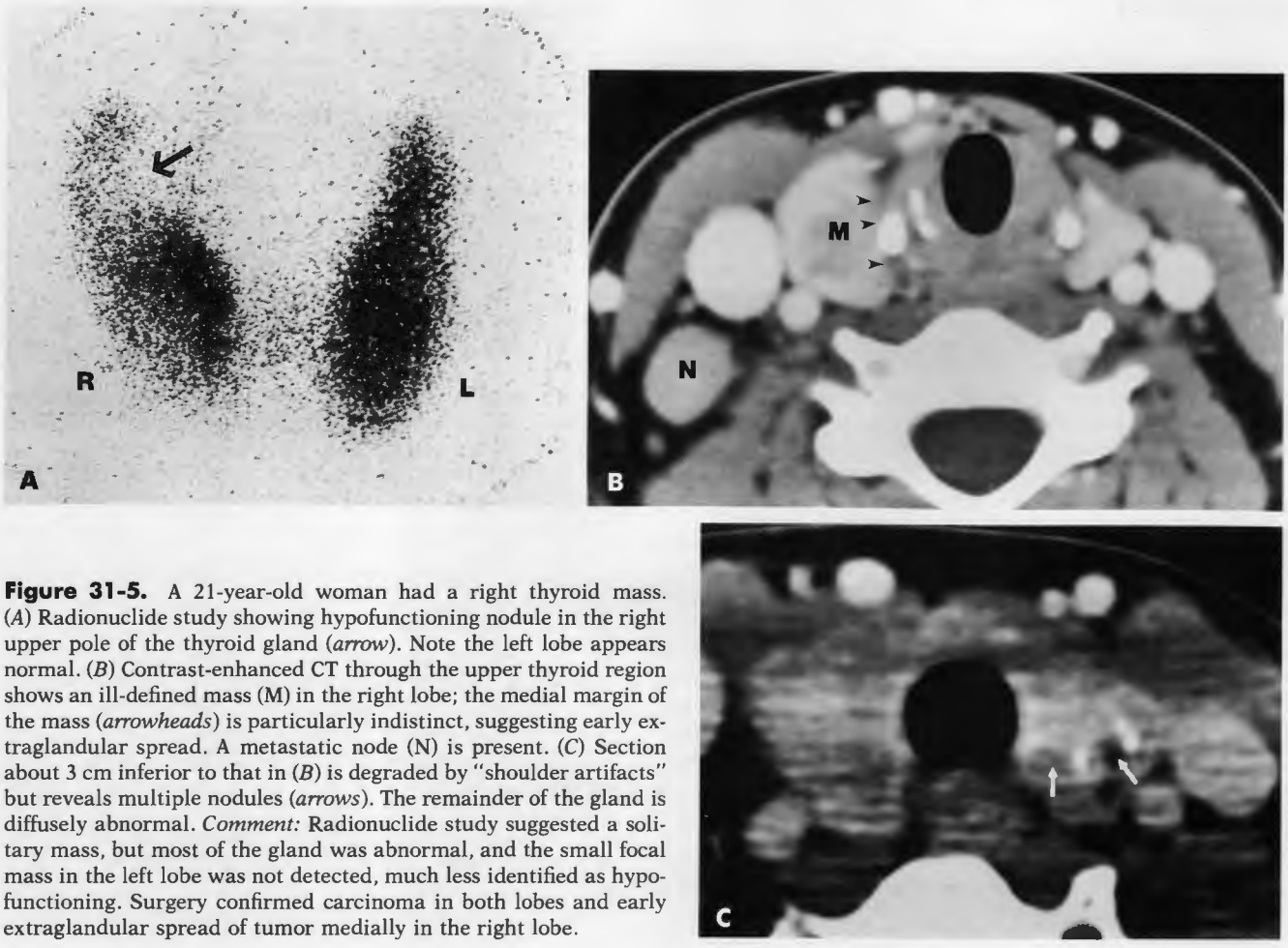

Figure 31-5. A 21-year-old woman had a right thyroid mass. (*A*) Radionuclide study showing hypofunctioning nodule in the right upper pole of the thyroid gland (*arrow*). Note the left lobe appears normal. (*B*) Contrast-enhanced CT through the upper thyroid region shows an ill-defined mass (M) in the right lobe; the medial margin of the mass (*arrowheads*) is particularly indistinct, suggesting early extraglandular spread. A metastatic node (N) is present. (*C*) Section about 3 cm inferior to that in (*B*) is degraded by "shoulder artifacts" but reveals multiple nodules (*arrows*). The remainder of the gland is diffusely abnormal. *Comment:* Radionuclide study suggested a solitary mass, but most of the gland was abnormal, and the small focal mass in the left lobe was not detected, much less identified as hypofunctioning. Surgery confirmed carcinoma in both lobes and early extraglandular spread of tumor medially in the right lobe.

Screening of High-Risk Populations

Calcitonin, a hormonal product of the cell of origin (the parafollicular or C cell) of medullary carcinomas, serves as a marker by which family members with C-cell hyperplasia (the presumed premalignant precursor of medullary carcinoma) or early, clinically inapparent medullary cancers can be identified.[156] Provocative testing is necessary because family members with early disease often have normal basal calcitonin levels but abnormal levels after stimulation.[130] Yearly screening after calcium or pentagastrin infusion has been recommended for family members over 5 years of age; a single screening is not sufficient because some who have a negative test initially are noted on follow-up to convert to a positive test.[156] Although such screening is not yet proven to increase the cure rate, almost certainly this will be the case because thyroidectomies are being performed in some very young, asymptomatic patients with very small primary lesions and no lymphatic metastases.[51,156] Screening of the relatives of 36 Mayo Clinic patients presumed to have the sporadic form of medullary thyroid carcinoma (ie, no family history of medullary carcinoma, pheochromocytoma, or hyperparathyroidism) resulted in detection of 57 new cases in seven families.[130] Thus, 19% of patients (7 of 36) presumed to have sporadic disease were actually index cases to kindreds with familial disease.

In addition to family members of patients with medullary carcinoma, another high-risk population that should be screened consists of patients known to have received low-dose irradiation during infancy and childhood. If the results of the baseline physical examination are normal, such patients should undergo careful reexamination every 1 to 2 years including ultrasound; ultrasound can detect nodules as small as 3 mm, and ultrasound-guided biopsy can be done on any suspicious area discovered. We do not recommend routine radionuclide thyroid scans in the absence of a palpable abnormality because these are unlikely to detect nonpalpable nodules under 2 cm in size. Compared with ultrasound, radionuclide scans are insensitive and, therefore, not cost-efficient. Moreover, ultrasound is noninvasive and is done without any radiation dose to the patient. Evaluation of thyroglobulin levels has little value as a screening procedure.[120] If a nodule is palpated, the patient generally proceeds directly to surgery.

Patients with a history of Hashimoto's thyroiditis should have an ultrasound yearly because of the high incidence of thyroid lymphoma that develops in these glands.

TREATMENT

Well-Differentiated Carcinomas

Surgery

There is still a difference of opinion among surgeons concerning how radical the thyroidectomy and node dissection should be. At the University of Florida, the operation is individualized according to the nature and extent of disease, with a tendency toward a fairly conservative surgical approach in the majority of cases; radioiodine therapy (and sometimes external-beam irradiation) are used for patients with a high likelihood of microscopic residual cancer. The minimum adequate operation is a total lobectomy, usually with resection of the isthmus. For patients with small intraglandular papillary carcinomas, low-grade encapsulated follicular carcinomas, or benign-appearing Hürthle cell lesions, this may be the only treatment necessary.[34] If a small, unsuspected cancer is found in a lobe resected for a benign condition, reoperation is usually not indicated. Similarly, if cancer was suspected but the frozen section was negative (eg, follicular adenoma), reoperation is usually not necessary after lobectomy if the pathologist later returns a diagnosis of minimally invasive follicular carcinoma on permanent sections.[57,66] Although there is disagreement among various specialists, there is no clear benefit from adding radioiodine to ablate the residual gland.[7] External-beam irradiation is not indicated.

If frozen section reveals follicular carcinoma with moderate to marked vascular invasion or if the tumor is larger, no matter what the histology, total or "near-total" (ipsilateral total and contralateral subtotal lobectomy) thyroidectomy is indicated. The presence of gross disease in both lobes calls for a total thyroidectomy.[34] If distant metastases are present, total thyroidectomy (or near-total thyroidectomy and radioiodine ablation of remaining gland) facilitates their detection and treatment with radioiodine.[7] Because the local and distant failure rates are high and the survival rate is low after thyroidectomy for markedly invasive follicular carcinoma,[34,63,161] adjuvant radiation therapy is recommended.

More advanced presentations require more extensive, individualized operations. The goal of surgical therapy is removal of all gross cancer with preservation of function whenever possible. If inadequate surgery has been performed, the most important first step in treatment is reoperation, if feasible. Unlike squamous cell carcinoma of the upper aerodigestive tract, invasive thyroid carcinoma can often be successfully resected with little margin of normal tissue; adjuvant external-beam irradiation, radioiodine therapy, or both are recommended.[84] The larynx, trachea, and recurrent laryngeal nerves are rarely sacrificed unless there is intraluminal tumor extension or such extensive involvement that conservative resection would leave behind gross tumor. If the strap muscles are invaded, they are removed en bloc with the gland. Tumors adherent to the trachea, larynx, and esophageal wall are most often "shaved off," after which external-beam irradiation, radioiodine therapy, or both are administered for microscopic residuum.[17,39,122] In some instances, partial resection of the trachea (resection and reanastomosis or tracheal window and reconstruction) or removal of a thyroid ala is necessary. If laryngeal paralysis has occurred, resection of the recurrent laryngeal nerve is required. Meticulous dissection of tumor off a functioning nerve is justified as long as no gross residual tumor remains.[84] Total laryngectomy along with resection of a length of trachea is rarely necessary for treatment of well-differentiated thyroid carcinoma.[14,15] In the presence of intraluminal invasion and hemorrhage, the necessity to control life-threatening hemoptysis may require laryngectomy, pharyngectomy, or tracheal resection. In rare cases, extensive invasion of the larynx and pharynx or of the esophageal wall with intraluminal extension may require total laryngopharyngectomy and esophageal resection with reconstruction by way of microvascular jejunal transfer or gastric pull-up.[84] If gross residual disease will definitely be left behind, operation is often best withheld; radioiodine therapy, external-beam irradiation, or both are administered in hopes of making disease resectable.

Gross evaluation of lymph nodes in the tracheoesophageal grooves and anterosuperior mediastinum should be made at the time of operation.[14,15] Resection of limited disease in the anterosuperior mediastinum can generally be accomplished through the cervical incision; attempts to resect more advanced disease necessitate splitting the sternum. Elective lymph node dissections are not routinely performed for papillary or follicular carcinoma. Suspicious nodes from the pretracheal region and tracheoesophageal groove are removed. If lateral neck nodes are involved, a modified neck dissection with preservation of the internal jugular vein, sternocleidomastoid muscle, and spinal accessory nerve is performed. Radical neck dissection is necessary in 10% or less of patients with papillary carcinoma,[7,160] usually only when tumor extends through the capsule of nodes. Although so-called lymph node plucking or berry picking procedures are performed by some surgeons, we prefer to do a modified neck dissection in the presence of gross nodal metastases, because it is a more complete operation and can be accomplished without functional loss. Local or regional recurrences are managed by completion thyroidectomy, neck dissections, or both as the need arises. If recurrent tumor extends into the soft tissues of the neck or if it is unresectable, external-beam irradiation and radioiodine therapy (if uptake is demonstrable) are added, because failure to achieve both distant[34] and local-regional control is frequent.

The treatment of choice for thyroid carcinoma arising in thyroglossal duct remnants is en bloc dissection of the cyst, including the midportion of the hyoid bone (Sistrunk procedure), and the entire thyroglossal duct because tumor may be present within the hyoid bone or at multiple sites within the duct.[69] Prognosis is favorable. Whether to perform thyroidectomy routinely is debated by various authors; it is our practice to do so.[69,76,143]

Suppression With Thyroid Hormone

Suppression of thyrotropin by administration of exogenous thyroid hormone has been reported to prevent recurrences after surgery and to result in temporary and occasionally permanent regression of metastatic well-differentiated thyroid cancer; the best results have been obtained in young patients.[34] In patients who have undergone a total or near-total thyroidectomy or who have had their glands ablated with radioiodine, administration of thyroid hormone is necessary just to meet physiologic needs. In patients who have remaining functional

thyroid tissue, thyroid hormone is administered for its suppressive effect. We recommend that thyroid hormone, in amounts sufficient to suppress thyrotropin, be administered indefinitely with interruptions only for radioiodine scans or treatments. Thyroxine (T_4) is usually used for suppressive therapy rather than triiodothyronine (T_3) because of its longer half-life (1 week versus 1 day) and because it is less likely to produce cardiovascular side effects.[28] The dose of thyroxine (eg, 200 to 300 μg) required to suppress TSH to low or undetectable levels is frequently larger than the dose required for replacement therapy alone.

Just as there is controversy over the surgery and radiation therapy for these tumors, so the role of thyroid hormone as a therapeutic agent remains controversial. Jesse and Clark[29,68] found no evidence for suppression of any type of thyroid cancer after administration of 3 grains of desiccated thyroid per day to over 700 patients who underwent total thyroidectomy at the M.D. Anderson Hospital. Likewise, Block[13] noted no apparent benefit from suppressive therapy after surgery for well-differentiated lesions. At the Lahey Clinic, there was a 5% reduction in death rate due to papillary cancer in those who received thyroid hormone postoperatively but no difference for follicular carcinoma.[21] In a review of 1578 patients with papillary or follicular cancers from 13 Canadian centers, Simpson and coworkers[128] concluded that, although thyroid suppression therapy did not significantly improve cause-specific survival in their multivariate analysis, almost every subgroup showed slightly better survival when given thyroid hormone and it should be used in all patients. Several other investigators who have tried to suppress gross disease with thyroid hormone have noted partial, short-lived regression in only a small percentage of patients, and usually not in all sites of involvement; eventual regrowth of tumor was noted in all cases.[52,125] The fact that some thyroid tumors are initially responsive to thyroid hormone, but later lose their responsiveness, is hardly surprising because this is routinely observed in other hormonally responsive cancers (eg, breast and prostate). Whenever treatment is indicated for known or suspected residual differentiated cancer, thyroid hormone should be administered only as a supplement to other therapy.[53]

Radiation Therapy

There are no precise guidelines for the use of external-beam irradiation or radioiodine therapy either alone or in combination for well-differentiated thyroid carcinoma. The subject is controversial. Any claims for the superiority of one technique over another are difficult to substantiate. The indications to use these treatments vary from center to center and often vary within a single institution. Controlled trials have not been performed, but they would require a large number of patients who could be carefully stratified according to a number of risk factors and have follow-up for many years.

Although postoperative external-beam irradiation is not used in most U.S. institutions, we believe that it does have a role in the treatment of a small percentage of patients with differentiated thyroid cancer. It is rational to use external-beam irradiation (usually after radioiodine treatment) in the following settings:

Extraglandular disease, because these patients are at the highest risk of developing locally recurrent disease that may ultimately lead to death due to airway obstruction[43,55,82,131,161]

Markedly invasive follicular carcinoma, because the rates of local and distant failure are both high[7,43,160]

Known gross residual cancer in the neck after operation.[125,144]

MICROSCOPIC RESIDUAL DISEASE. For many patients, routine ablation of remaining thyroid tissue with radioiodine or external-beam irradiation represents overtreatment after adequate surgery because cure has usually already been achieved;[85] this is particularly true of patients under 40 years of age in whom no residual tumor is thought to remain after operation and who have no histologic evidence of extraglandular extension.[22,128] Among 237 patients with intrathyroidal papillary carcinoma of the thyroid who were treated with conservative surgery (mostly lobectomy) without radioiodine at the Massachusetts General Hospital between 1931 and 1970, the 20-year probability of tumor recurrence was 6.9%; only two patients died of thyroid cancer (at 14 and 20 years).[153]

Although the risk of developing acute leukemia after treatment with iodine-131 (^{131}I) is admittedly small (less than 1%), the risk is considered by some to contraindicate its routine prophylactic use in patients who have little risk of tumor recurrence. Others argue that because of its safety and the proven efficacy of ^{131}I in young patients, near-total thyroidectomy and ^{131}I ablation is a more rational therapy than total thyroidectomy without ^{131}I. Total thyroidectomy places the patient at a 15% to 20% risk of permanent hypoparathyroidism, the management of which is laborious, inconvenient, and lifelong.[49] In our own institution, patients younger than 40 years of age with small (1.5 cm or less) intraglandular papillary carcinomas generally are treated by lobectomy and isthmusectomy without radioiodine. The remaining patients less than 40 years old and all patients greater than 40 years old usually receive ^{131}I ablation of residual glandular tissue.[145]

Radioiodine ablation of remaining normal thyroid tissue aids in detection of distant metastases; normal residual thyroid tissue takes up ^{131}I much more avidly than does the tumor, so it must first be ablated. If a large volume of normal thyroid gland remains, it is generally removed by completion thyroidectomy because ablation of an entire lobe requires administration of large doses of ^{131}I.

Radioiodine is administered when microscopic disease is known to remain, unless tumor does not concentrate it. If all residual tumor avidly and uniformly takes up radioiodine, a radiation dose of many thousands of centigrays may be delivered to the tumor; unfortunately, uptake is not always present or uniform.

Patients with extensive (extraglandular) local disease require aggressive local treatment because they are at significant risk of local failure; in these patients, a combination of radioiodine therapy and external-beam irradiation is used at the University of Florida. Support for an aggressive approach comes from a number of institutions. In the Mayo Clinic series, Smith and coworkers[131] noted that patients with recurrent laryngeal nerve paralysis, tracheal or esophageal invasion, or muscle or soft tissue invasion were all at significantly increased risk of death from papillary cancer, and that the most common cause of death was local tumor (airway obstruction or hemorrhage). Almost all (86%) of those patients who had

extraglandular extension and who suffered a local recurrence died as a result of thyroid cancer.[85] Carcangiu and coworkers[22] noted that extrathyroidal extension was associated with markedly decreased freedom from disease and markedly increased probability of death due to cancer; death in most patients was due to uncontrolled tumor in the neck, with progressive encirclement of the trachea and other vital structures. The risk of death due to distant metastases was not increased.

Bacourt and coworkers[5] performed a multivariate analysis on 375 patients with differentiated thyroid cancer. All patients were treated by total thyroidectomy and ^{131}I. All had from 5 to 23 years of follow-up. The administration of ^{131}I to all patients was not sufficient to eliminate local disease extent as the most significant prognostic factor for survival.

The Institut Gustave-Roussy, the Princess Margaret Hospital, the Royal Marsden Hospital, and the Glasgow Institute of Radiotherapeutics have considerable experience in combining external-beam irradiation with radioiodine therapy[52,55,125,147] in patients with, or at high risk of developing, both local and distant failure.

It has been argued that external-beam irradiation is contraindicated because it may prevent radioiodine concentration. Support for this notion comes largely from a case report published over 40 years ago.[106] In the series of Carr and associates,[23] the concentrating ability of ^{131}I was not adversely affected by external-beam irradiation. All 13 patients who had received external-beam treatment before ^{131}I showed good uptake by tumor, and almost all experienced complete regression of disease.[23] Halnan[53] also noted that x-ray therapy usually did not inhibit iodine concentration.

Radioiodine therapy is not always effective in eradicating small volumes of local disease or in preventing distant metastases, even when tumors initially show good concentrating ability. Uptake may be nonuniform.[23] In many instances, tumors lose the ability to concentrate radioiodine after successive doses, or recur in spite of uptake.[61,78] Maheshwari and associates[78] noted that patients who required successive doses of radioiodine or cumulative doses exceeding 300 mCi were infrequently cured.

The magnitude of improvement in survival due to ^{131}I therapy is difficult to assess. Beierwaltes' data (as in Varma and associates[151]) are most often quoted and present several problems. Conventional survival and disease-free survival calculations (eg, at 5 or 10 years) were not given. Only "death rates" (total dead divided by number treated) were reported; these figures are biased by inclusion of patients with less than 3 months of follow-up. The control group (no radioiodine, 1933 to 1947) had longer follow-up, had less aggressive surgical resections, contained an unspecified number of patients with distant metastases, and was composed largely (64%) of patients over 40 years of age (of the ^{131}I-treated patients, only 32% were over age 40). The cause of death in control patients was unknown in most instances. Although death rates were lower in the ^{131}I-treated group, factors other than ^{131}I may have been responsible.

When tumor has been shaved off the larynx, trachea, or esophageal wall by sharp dissection, residual microscopic disease is presumably present. Both radioiodine therapy and external-beam irradiation may prevent local recurrences; at the University of Florida, both treatments are usually applied because the risks of both local and distant failure are substantial,[125] and both treatments can be delivered safely. Sheline[122] reported excellent results in a small series of well-differentiated thyroid cancers treated with external-beam irradiation (5000 to 6000 cGy over 6 to 7 weeks) after microscopically incomplete resection (Table 31-2). Simpson and coworkers[128] showed that postoperative irradiation by itself or with radioiodine therapy led to improved rates of local control and cause-specific survival. Benker and colleagues[11] suggested that external irradiation is a valuable addition to radioiodine therapy in patients over the age of 40 with locally advanced (T3 to T4) primary cancers; the 10-year survival rate in 100 patients who received radioiodine and thyroxine after operation was 50% compared with 67% in 144 patients who received radioiodine, thyroxine, and external-beam irradiation (4000 to 7000 cGy; $P = .09$). Wu and coworkers[162] noted significantly (P less than .05) improved 5-year survival among 108 patients with microscopic residual disease when 5000 to 7000 cGy was administered postoperatively compared to patients treated by surgery alone. When analyzed according to a variety of prognostic factors (soft tissue or skin invasion; involvement of the esophagus, trachea, larynx, hypopharynx, nerves, large blood vessels; primary fixation; and primary larger than 18 cm), external-beam irradiation improved the survival rate in each subgroup. External-beam irradiation was effective in both previously untreated and recurrent tumors. Tubiana and coworkers[146] showed that in 154 patients with incomplete surgery, the rate of local recurrence was 32% after surgery alone compared to 15% after surgery and 5000 cGy postoperative irradiation (P less than .05). The usual dose recommended for microscopic residual disease at the University of Florida is 6000 cGy over 6½ to 7 weeks.

GROSS RESIDUAL DISEASE. External-beam irradiation is indicated if there is unresectable gross residual cancer after operation or if local disease is inoperable. Radioiodine therapy alone is usually insufficient to control large masses in the neck, even when the tumor concentrates the substance.[125,144] Moreover, in approximately 20% of cases, the tumor does not concentrate ^{131}I.[55] A combination of the two treatments is advised;[52,55,125,144] there are no data to show how best to time one treatment relative to the other or to guide the doses of each modality. In very advanced cases, only palliation is to be expected. Regression of gross disease after radiotherapy may continue for several months.

Six of 10 patients treated at the University of California, San Francisco, with postoperative external-beam ir-

TABLE 31-2. Local Control After External-Beam Irradiation for Papillary or Follicular Carcinoma After Microscopically Incomplete Resection

Histology	Local Control/Treated
Papillary	12/12
Follicular	3/5
TOTAL	15/17 (88%)*

* Length of follow-up in patients with locally controlled disease was 5 to 22 years (mean 10.2 years; median 9 years). Local recurrences in two patients occurred at 4 and 6 years.

Note: University of California, San Francisco, data from Sheline and associates.[122]

radiation for macroscopic residual disease remained locally controlled for 5 to 25 years; even when treatment was unsuccessful, palliation was often substantial, because all four of the failures occurred 5 to 18 years after treatment.[122] Survival at 15 years after postoperative external-beam irradiation of gross residual cancer was 36% at the Institut Gustave-Roussy.[144,147] Chung and coworkers[27] showed the value of external-beam irradiation in a small group of patients with well-differentiated tumors that did not take up ^{131}I; in 3 of 8 patients, palpable residual disease remained controlled at 4 to 7 years.

INOPERABLE TUMORS. The results of external-beam irradiation alone for inoperable tumors have not been highly satisfactory, but prolonged palliation is sometimes achieved. Frazell and Foote[46] reported that 6 (26%) of 23 patients with advanced, inoperable primary or recurrent papillary cancer were without evidence of recurrence 5 years after x-ray therapy alone. In a larger series of patients, Tubiana[144] reported 20% of patients with inoperable tumors alive 5 years and 10% alive 15 years after external-beam irradiation. Simpson and colleagues[128] likewise noted local control in approximately 20% of patients with gross cancer (4 to 24 years of follow-up) who received treatment with external-beam alone as opposed to approximately 50% in those whose tumors concentrated radioiodine and a somewhat higher percentage when both radioiodine and external-beam irradiation were used. Combined treatment is indicated if the tumor concentrates radioiodine.

HÜRTHLE CELL TUMORS. Hürthle cell neoplasms do not concentrate radioiodine. However, some authors recommend its use to ablate small amounts of tumor that may remain in the thyroid remnant and to ablate the remaining normal gland so that thyroglobulin may be used as a tumor marker in follow-up.[2] The role of external-beam irradiation as a postsurgical adjuvant for patients with advanced local-regional disease is unclear. In light of the fact that radioiodine is not taken up by the tumor and that the tumors are responsive to palliative doses of irradiation,[54] external-beam treatment would seem logical in patients who have microscopic residual disease.

EXTERNAL-BEAM IRRADIATION TECHNIQUE. It is a technical challenge to deliver high-dose external-beam irradiation to the thyroid, trachea, cervical esophagus, jugular lymph nodes, upper neck, and upper mediastinum without exceeding spinal cord tolerance. The depth of the spinal cord from the anterior skin surface varies markedly in this anatomic region because of differences in thickness between the upper chest and low neck. From a lateral approach, the contour is even more irregular, because of the shoulders. Because of these difficulties the doses of external-beam irradiation applied in some series have been low.[83] There is no evidence that thyroid carcinomas are more or less curable by external radiotherapy than squamous cell carcinomas of equal volume; their response is considerably slower.[128] For most situations in which radiation therapy is indicated, high doses (eg, 6000 to 7000 cGy over 6½ to 7½ weeks) are required. A number of techniques have been devised to deliver a high dose to this region, including high-energy electrons, oblique wedges, and rotation. The normal cervical lordosis and thoracic kyphosis make rotational treatment impractical because the technique does not allow adequate field-shaping. Simple lateral fields do not allow adequate dosage of the upper mediastinum because the shoulders are in the way. Exclusive use of high-energy electrons has the disadvantages of excessive subcutaneous fibrosis and underdosage in the mediastinum. Anterior (AP) and posterior (PA) portals, usually weighted in favor of the anterior portal, can be used to deliver the initial 5000-cGy tumor dose to the low neck and upper mediastinum.[75] Boost doses beyond 5000 cGy may be administered with electrons in some situations. If doses in the range of 6000 to 6500 cGy are required in the upper mediastinum, a four-field box technique using compensated (with beeswax) lateral fields has generally been used at the University of Florida (see Chap. 21). Three-dimensional treatment planning with angled wedges may be a reasonable option. Neck disease behind the plane of the spinal cord can be treated with electrons.

RADIOIODINE TECHNIQUE. Ablation of thyroid remnants is usually done 6 weeks after surgery; the usual dose is 100 to 200 mCi of radioiodine, administered orally. Whole-body imaging is done before ablation.

Approximately 6 months after ablation, whole-body imaging (4 to 10 mCi ^{131}I) is performed to assess completeness of ablation and search for local-regional or distant metastatic thyroid cancer. As a general rule, metastases do not concentrate radioiodine if normal thyroid tissue is present. To maximize uptake of radioiodine in thyroid remnants and metastatic lesions, TSH levels need to be elevated. A commonly used method is to withdraw thyroid hormone replacement before the scan. Exogenous thyrotropin is not routinely administered because it provides little or no additional benefit if the patient has been off thyroid hormone for sufficient time; in addition, some patients develop allergic reactions to exogenous TSH. Thyroxine (T_4) is discontinued for 6 weeks; in many patients, triiodothyronine (T_3) in doses of 75 to 100 μg is substituted for thyroxine for the first 3 weeks after thyroxine is discontinued, to limit the duration of symptomatic hypothyroidism. This procedure is particularly useful in the occasional patient whose tumor grows rapidly when a hypothyroid state is established. (In the latter group of patients, T_3 is usually discontinued 2 weeks before the scan; exogenous TSH is administered if endogenous TSH levels are not sufficiently elevated.) Serum TSH is measured before scanning to verify a significant hypothyroid state (optimally, TSH greater than 65 mCiU/mL). If the level is insufficient, either the scan is delayed or exogenous TSH is administered. If thyroid cancer that is capable of concentrating radioiodine is detected, treatment with radioiodine (usually 200 mCi) is administered. Retreatment is given at 6-month intervals if continued uptake is demonstrable. After a cumulative dose of 600 mCi has been reached, pulmonary function tests are obtained (even in patients without lung metastases) before further radioiodine treatments are administered, to rule out the possibility of pulmonary fibrosis.

Because iodinated contrast medium (as used in CT scanning or intravenous pyelography) severely interferes with radioiodine uptake, these tests should not precede radioiodine scanning. Typically, one must wait 4 to 6 weeks after administering intravenous contrast material before performing a radioiodine scan.

Thyroid hormone replacement may be resumed 3 days after radioiodine treatment or immediately after completion of diagnostic studies.

Follow-Up

Patients at risk for recurrence in the low neck, thoracic inlet, and superior mediastinum are best observed by CT or MRI. MRI is preferred because it is better than CT for distinguishing posttherapy scar from residual tumor, does not interfere with radioiodine uptake, and allows multiplanar imaging. Periodic whole-body radioiodine scans are useful in monitoring patients at high risk of developing recurrence and may detect abnormalities that are not detectable with other radiographic studies. Our recommendation is radioiodine ablation of normal gland 6 weeks after surgery, followed by a metastatic survey in 6 to 9 months, then annually thereafter. When two normal surveys are obtained at a year apart, the scanning interval is extended to 2 years. Follow-up is lifelong because there remains some risk of recurrence even 30 or more years after treatment.[148] Chest films are obtained annually. Technetium bone scans and bone surveys are not performed in the absence of symptoms. Serum thyroglobulin is of value in detecting recurrent cancer in patients whose glands have been totally removed or ablated.[150] Because thyroid tissue is the only source of circulating thyroglobulin, patients who have no residual normal thyroid tissue should have no detectable serum thyroglobulin except that which is produced by persistent cancer. The diagnostic accuracy of thyroglobulin determination is not satisfactory if normal residual thyroid tissue is present.[119] The test is particularly valuable in the follow-up of patients with nonfunctioning tumors. We generally obtain thyroglobulin measurements at the same time as radioiodine scans[32] because the thyroglobulin assay is more sensitive in the hypothyroid state. The measure of thyroglobulin provides information that is complementary to radioiodine scans because disease detection may be possible by only one or the other technique. Occasional patients have metastases detectable only by chest roentgenogram, their scans and sera being normal.[42,50,103,107]

Although not as specific as ^{131}I, thallium (^{201}Tl) scintigraphy has been shown to detect distant metastases in a high proportion of cases. Thallium is more sensitive than ^{131}I but may be concentrated by abscesses and by other tumor types. In the clinical setting of patients with known thyroid cancer, this potential nonspecificity is less relevant.[19,104] The test is particularly useful in patients whose tumors do not concentrate ^{131}I. Several patients have been reported whose tumors were detectable with thallium but not radioiodine.[19,64] Scintigraphy using thallium rather than radioiodine has several advantages in that it does not require discontinuation of thyroid hormone[124] and can be performed immediately after injection (compared with radioiodine scans, which are usually performed 3 days after oral administration). Single photon computed tomography (SPECT) imaging has been reported to improve detectability of thyroid cancer metastases by thallium, especially in the low neck and mediastinum, compared with planar imaging; coronal sections were best for this purpose.[25]

Chemotherapy

Shimaoka and coworkers[123] reported the results of an Eastern Cooperative Oncology Group (ECOG) trial in which 35 patients with metastatic or locally unresectable differentiated thyroid cancer were treated with either doxorubicin or doxorubicin plus cisplatin after tumor had become resistant to radioiodine and thyroid hormone suppression. Complete (two patients or 6%) or partial (six patients or 17%) remissions were observed in 23% of the patients. The duration of both complete responses was greater than 2 years; both occurred in the group of 19 patients who received cisplatin plus doxorubicin.

Treatment of Distant Metastases

Approximately 50% of metastases can be made to concentrate radioiodine and produce a favorable response.[12,61,81,92,105] Not all lesions that concentrate ^{131}I regress, because its concentration may be poor, its distribution nonuniform, or the tumor poorly responsive.[132] In patients with multiple sites of disease, not all lesions take up ^{131}I to the same degree.[121] Five percent to 10% of all patients with distant metastases from well-differentiated carcinomas are believed to be permanently cured after administration of radioiodine;[21,65,144] in patients with lung metastases only, the cure rate may be as high as 30% if the tumor concentrates radioiodine.[92,144] In some patients who were presumed to have been cured and who died of other causes, autopsies have disclosed residual thyroid cancer.[145] If radioiodine is not taken up, long-term survival is unusual. Most of the patients in whom treatment is successful are under 40 years of age.[59,85,92] Most series report that papillary and follicular lesions show no difference in concentrating ability. Concentration of radioiodine by invasive follicular carcinoma is sometimes poor.[144] Treatment in most patients is only palliative in intent, but is undertaken even in the absence of symptoms because all clinical evidence of disease may disappear for substantial periods of time.[82]

The best long-term results are achieved in patients with diffuse miliary lung disease. Miliary (or micronodular) lung metastases typically appear as tiny densities predominantly in the lower lung fields or as a diffuse reticular pattern.[81] In some patients, chest roentgenograms are normal and functioning lung metastases are proven only by radioiodine total-body scan; CT is able to demonstrate small peripheral nodules in some patients.[101] Patients with micronodular disease tend to be young, have papillary disease, have tumors that take up ^{131}I, usually have cervical lymph node metastasis, tend to present with metastases at the time of diagnosis or soon thereafter (within 1 year), and have a relatively good prognosis[78,81,92] compared to patients with macronodular disease.[49,65] Because patients with diffuse lung involvement are the group most likely to develop severe or fatal radiation pneumonitis or pulmonary fibrosis, large single doses of ^{131}I are to be avoided (Sheline GE. Personal communication, September, 1982).

Patients over 40 years of age who present with or develop pulmonary metastases after ^{131}I treatment have a poor prognosis. About half of those whose tumors take up ^{131}I respond, and, of those, most recur.[78] Consideration should be given to surgical resection of a solitary pulmonary metastasis, followed by ^{131}I scan and therapy. Disappearance of lung nodules after ^{131}I therapy is no guarantee of cure, because they may recur and progress.[105]

In a series of 58 patients with pulmonary metastasis from well-differentiated thyroid carcinoma, Massin and coworkers[81] noted that 55% of patients had tumors that took up ^{131}I (86% uptake for micronodular versus 43% for macronodular disease). Patients under age 30 had consistently positive uptake. No differences in uptake were

noted between papillary and follicular disease. Overall 10-year survival rates from this and other series are 15% to 20%. The 8-year survival rate for patients with micronodular disease (representing about one third of all patients with pulmonary metastasis) was 77% versus 18% for patients with macronodular disease without mediastinal metastases and 9% for patients with both macronodular disease and mediastinal lymph nodes. These results are similar to those of Nahemec and coworkers,[92] who further reported that in patients in whom uptake was induced, the 10-year survival was 70% versus 6% for patients whose tumors did not take up ^{131}I. Survival was poor if bone metastases were also present. In some patients, pulmonary metastases follow a slow course without treatment.

Beierwaltes and coworkers[9] reported 20-year survival rates of 25% to 35% after radioiodine therapy in 103 patients with follicular or papillary cancer metastatic beyond the neck. Actual cure rates were lower because the series included patients treated through the date of analysis. Inclusion of patients with short follow-up elevates the survival curve. Fifteen (26%) of 57 survivors were not disease-free. Furthermore, survival was calculated from the date of diagnosis of cancer, rather than the date of metastasis; some patients who developed late metastases were therefore scored as 10- and 20-year survivors of metastases when the metastatic event had not yet occurred. The survival rates in patients whose tumors were detectable only by radioiodine scan, but not by roentgenograms, were likewise not stated.

Benua and coworkers[12] reported the Memorial Hospital results in 59 patients with metastatic differentiated thyroid cancer. A total of 122 doses of ^{131}I were given (average dose, 194 mCi). Sustained objective remissions were noted in 16 patients (27%); minimum follow-up was 1 month.

Patients with bone metastases are often older than 40 and have tumors that concentrate radioiodine poorly;[59,78] even if the tumor concentrates radioiodine and disappears, recurrence is the rule.[8] Patients rarely survive long periods without recurrence.[56,147,160] Patients with metastases to weight-bearing long bones or vertebrae and patients with bone pain should be given external-beam irradiation in addition to radioiodine;[78,91] orthopedic fixation is sometimes necessary.

Medullary Carcinoma

Because of the high incidence of multicentricity and bilaterality within the gland, total thyroidectomy is recommended.[7,74] If parathyroid hyperplasia is also present, all parathyroid tissue is removed and a portion of one gland is autografted.[155]

In patients without apparent lymph node metastases, the central lymph nodes between the carotid sheaths from the hyoid bone to the innominate artery are dissected. If there is obvious lymphadenopathy, or if frozen section reveals positive lymph nodes, unilateral or bilateral neck dissections are performed.[7,26,74,89] When patients with positive nodes are treated by operation alone, clinical failure occurs in almost two thirds of cases, and a number of others are presumed to have residual disease on the basis of persistently elevated calcitonin levels.[26] Because most failures occur in the mediastinum and neck, postoperative irradiation should be given to patients with positive lymph nodes. Medullary carcinomas do not concentrate radioiodine and are not suppressed with thyroid hormone.

When doses of external-beam irradiation similar to those used for squamous cell carcinoma are used postoperatively, small amounts of residual tumor have been controlled.[52] At the Institut Gustave-Roussy, only patients with unfavorable tumors (lymph-node involvement or inadequate surgical excision) were given postoperative irradiation; their survival rate at 20 years was higher than that of patients with less advanced cancers treated by surgery alone.[114] There are several reports of patients with gross or inoperable masses whose disease was controlled (with 8 to 17 years of follow-up) by high-dose irradiation.[52,112,147] Regression of gross disease occurs slowly.

Patients are monitored 1 to 2 weeks postoperatively, then every 6 to 12 months, for elevated calcitonin levels. Postoperatively, the calcitonin level usually falls sharply when the disease is thought to be extirpated, but the nadir is sometimes not reached for several months.[135] Carcinoembryonic antigen levels may provide additional useful information.[113] Norton and coworkers,[97] at the National Cancer Institute, studied seven asymptomatic patients who had no clinical signs of disease and negative metastatic work-ups but who had elevated basal or stimulated calcitonin levels 1 to 5 years after thyroidectomy. By performing selective venous catheterization with pentagastrin stimulation, he was able to locate disease in the neck or superior mediastinum in all seven; in each patient, the presence of residual cancer was histologically confirmed. After resection, calcitonin levels returned to normal in only one patient.

Selective venous sampling is invasive, time consuming, labor intensive, and expensive; it is little used today.[149]

When calcitonin levels are elevated and the site of residual disease is unknown, patients are screened with ^{201}Tl and DMSA(V) whole body scans. These scans may locate tumor deposits and monitor the effectiveness of subsequent therapy.[3,31,64,137,149]

Shimaoka and coworkers[123] reported results of an ECOG trial in which 10 patients with unresectable or metastatic medullary carcinoma were treated with doxorubicin or doxorubicin plus cisplatin. Three patients had a partial remission that lasted less than 2 years. There were no complete responders.

Anaplastic Carcinoma

Anaplastic carcinoma is one of the most aggressive human neoplasms. Most patients have advanced, incurable disease at presentation. Regardless of treatment type, cure is rare. Anaplastic carcinoma does not concentrate radioiodine, does not suppress with exogenous thyroid hormone, and responds poorly to external-beam irradiation, often growing during treatment.[122] The tumors are usually locally unresectable at presentation; laryngectomy, pharyngectomy, cervical esophagectomy, and radical neck dissections are rarely justifiable. The usual intent of treatment is palliation of local symptoms. Tracheostomy is often necessary to prevent death by asphyxiation and must often be carried out with the use of a bronchoscope to ensure an adequate airway while a search is made for the trachea in the midst of a massive local tumor. Operative deaths have been described in

this setting.[39] External-beam irradiation is administered to palliate symptoms of local or metastatic disease.

For patients with resectable lesions, total thyroidectomy is followed by external-beam irradiation, even when resection is considered complete. The best chance for cure is in the occasional patient who has a small focus of anaplastic carcinoma within a predominantly well-differentiated carcinoma;[1,7] external-beam irradiation is recommended postoperatively.

Treatment of extensive local disease is often by radiation therapy alone. In patients who are otherwise in reasonably good medical condition, efforts are made to avert a miserable death secondary to local disease. Combinations of chemotherapy and irradiation may produce better results than irradiation alone; attempts to combine the two modalities must be made with caution to avoid excessive side effects.[136] Because these tumors proliferate rapidly, use of accelerated fractionation schemes is logical.

Shimaoka and coworkers[123] reported the results of an ECOG trial in which 39 patients with unresectable or metastatic anaplastic carcinoma were randomly assigned to receive doxorubicin or doxorubicin plus cisplatin. Complete (three patients) or partial (four patients) response was achieved in 18% of patients. Two of the three complete responses were of greater than 2 years' duration; all three complete responses occurred in the group that received doxorubicin and cisplatin. Partial responses were of brief duration.

RESULTS OF TREATMENT

Well-Differentiated Carcinomas

Differentiated carcinomas often have a long natural history; 5 years is insufficient time to assess treatment results. At the Lahey Clinic,[21] approximately half of all recurrences and cancer deaths occurred after 5 years (Figs. 31-6 and 31-7). Tumor recurrence and death due to cancer continued to occur sporadically up to 25 and 30 years, respectively, after treatment. In the Institut Gustave-Roussy experience, 25% of first recurrences occurred after 20 years.[148]

The following factors correlate with a decreased rate of survival:

- Age over 40.[21,127,138,148,160]
- Extension of the primary lesion through the capsule of the gland or of nodal metastasis through the capsule of the lymph node into surrounding soft tissues.[21,22,127,131,138,160] In two large multivariate analyses, local disease extent was the most important prognostic factor[5,138] and in one study was as important as distant metastasis at diagnosis.[5]
- Follicular carcinoma with moderate to marked invasiveness. Most authors have found that patients with follicular tumors have lower survival rates than patients with papillary cancer.[10,34,63,116,127,138,161]
- Large size of the primary lesion[127,160]
- Male sex[18,20,21,46,127,139]
- Distant metastases[21,127,144]
- Marked cellular atypia[5,138]

Not all of the variables are independent of one another; for example, the most aggressive histologic types tend to occur in patients with large primary lesions.[17] Lymph node metastasis has been shown to be of no prognostic significance in a number of large series. Most nodal presentations are successfully managed by initial surgery; salvage surgery is usually successful when initial surgery fails.[21,30,83,133,159] An inverse correlation between the presence of nodal metastasis and death due to cancer has at times been demonstrated, with the highest rates of survival in patients with the greatest number of positive nodes. This is a reflection of the fact that a high proportion of young patients (who have an excellent prognosis) present with nodal metastasis from papillary cancer.[21,63] In a multivariate analysis of 1578 patients, Simpson and colleagues[127] found that the most important prognostic factor for cause-specific survival among patients with papillary cancer was age, followed by extraglandular extension; for patients with follicular cancer, extrathyroidal extension was the most important prognosticator.

Radiation-induced thyroid cancer behaves no differently than that which occurs sporadically.[41,85,117] For papillary carcinoma, the relative proportions of the pap-

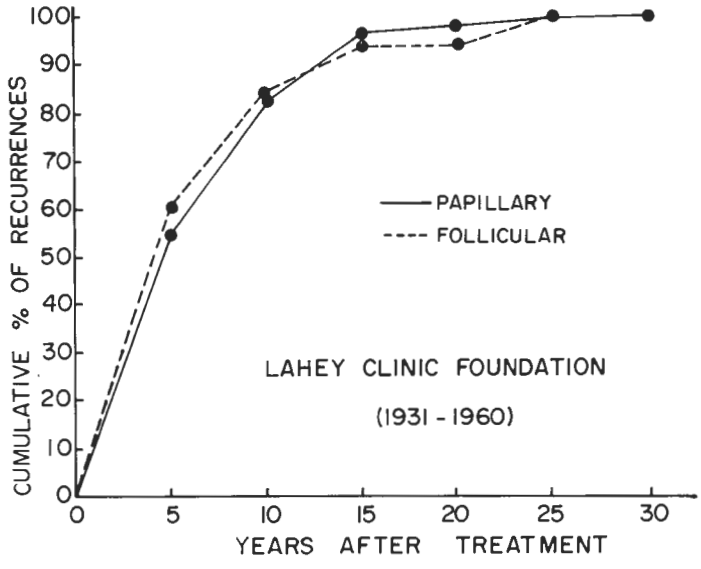

Figure 31-6. Cumulative percentage of recurrences of differentiated thyroid carcinoma (Lahey Clinic Foundation, 1931–1960). In the papillary group, first recurrences were local or regional in approximately one half of cases, whereas in the follicular group, the first recurrence was most often (75%) distant metastasis. (Data from Cady B, Sedgwick CE, Meissner WA, Bookwalter JR, Romagosa V, Werber J. Changing clinical, pathologic, therapeutic, and survival patterns in differentiated thyroid carcinoma. Ann Surg 1976;184:541–553)

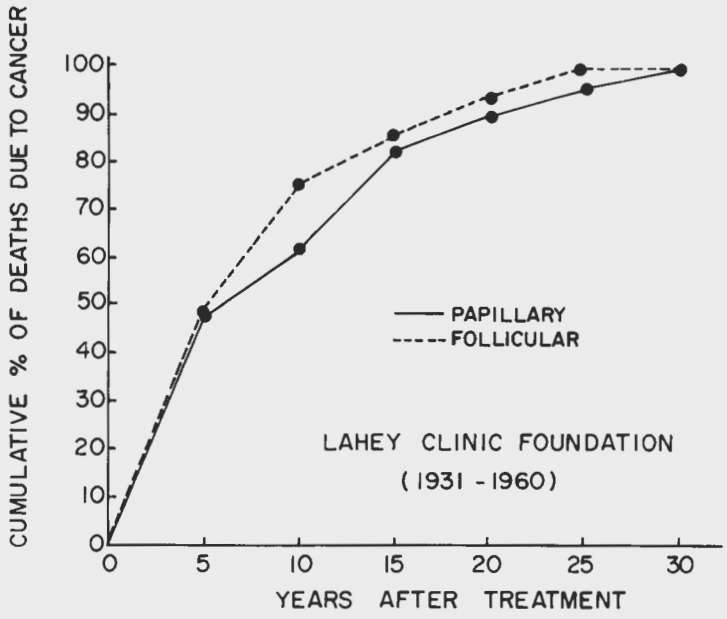

Figure 31-7. Cumulative percentage of deaths due to differentiated thyroid carcinoma (Lahey Clinic Foundation 1931–1960). Slightly fewer than half of the patients who died of thyroid cancer did so by 5 years. (Data from Cady B, Sedgwick CE, Meissner WA, Bookwalter JR, Romagosa V, Werber J. Changing clinical, pathologic, therapeutic, and survival patterns in differentiated thyroid carcinoma. Ann Surg 1976;184:541–553)

illary and follicular elements are of no apparent significance; multiple foci of tumor within the gland are common but have not been shown to affect prognosis adversely.[33] It is difficult to assess the effect of any individual mode of treatment on survival because adjuvant treatments (eg, radioiodine, external-beam irradiation, and thyroid hormone) are seldom used alone and have seldom been applied in any systematic manner for similar stage disease.

Papillary Carcinoma

At the Mayo Clinic, intraglandular papillary carcinoma less than or equal to 1.5 cm has been arbitrarily designated as "occult" whether clinically apparent or not. Hubert and coworkers[66] reviewed results of conservative operations in 137 patients with occult lesions. In 82 patients, the operation was performed for a coexisting condition (eg, multinodular goiter, Graves' disease); cancer was unsuspected. In most of the remaining 55 patients, the presentation was that of neck node metastasis without evidence of a primary tumor; in many, the enlarged nodes were massive. Surgery usually consisted of unilateral or bilateral subtotal lobectomy; no total thyroidectomies were performed. In 55 patients with lymph node involvement, modified neck dissection or excision of palpably involved nodes was usually performed. Only two radical and no elective lymph node dissections were performed. Ten (18%) of 55 patients with positive lymph nodes required reoperation (13 total operations) for recurrence; all disease was resectable by conservative lymphadenectomy or completion thyroidectomy. Two (5%) of 82 patients with negative lymph nodes underwent reoperation for primary tumor recurrence; none required lymph node dissection. With 25 to 54 years' follow-up, 1 patient (0.7%) died of thyroid cancer. Such patients do not require radical operations, external-beam irradiation, or radioiodine on the basis of possible multicentric disease or residual nodal disease. Although 10% of patients required reoperation, the salvage rate was high. The recommended treatment is ipsilateral total and contralateral subtotal lobectomy, judicious nodal surgery, and replacement thyroid hormone.

The survival rate for patients with intraglandular tumors larger than 1.5 cm was almost as good as in the group with occult tumors; with 11 to 40 years of follow-up, 8 (3%) of 272 patients died of cancer. The 20-year survival rate of patients with extraglandular extension was half that of the other two groups (Fig. 31-8).[161] In Simpson and McKinney's[126] review of 1062 patients with papillary carcinoma, the overall 20-year survival rate was approximately 66%; the cause-specific survival rate at 20 years was 81% (ie, approximately half of all deaths were due to thyroid cancer). In a separate review of 844

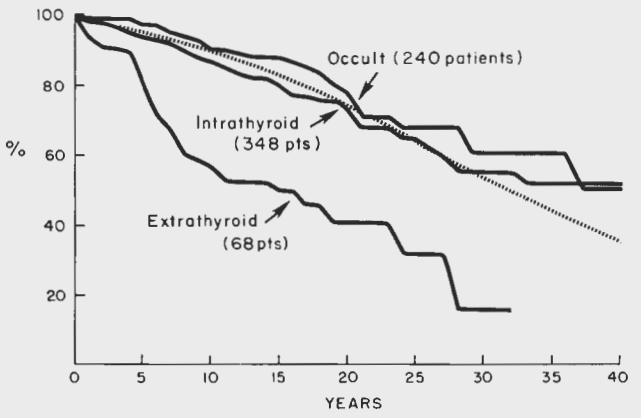

Figure 31-8. Survival after treatment of 656 patients with papillary carcinoma of the thyroid gland (Mayo Clinic, 1926–1960). The "occult" group comprises patients whose primary lesions were less than or equal to 1.5 cm in size. The dotted line represents survival of normal people of comparable age and sex. (Woolner LB, Beahrs OH, Black BM, McConahey WM, Keating FR. Thyroid carcinoma: general considerations and follow-up data on 1181 cases. In: Young S, Inman DR, eds. Thyroid neoplasia. New York, Academic Press, 1968:58)

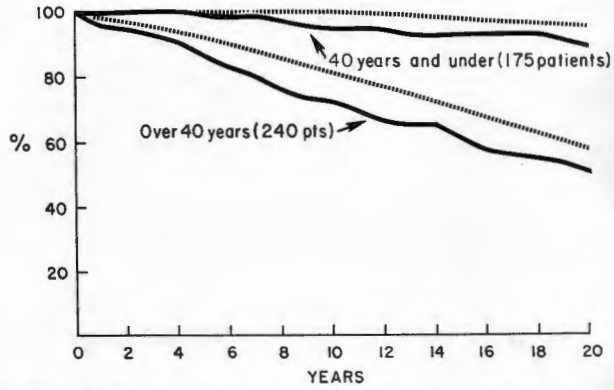

Figure 31-9. Survival after treatment of 415 traced patients with papillary carcinoma of the thyroid gland (Mayo Clinic, 1926–1960). Excluded are patients with lesions less than or equal to 1.5 cm (ie, "occult" carcinomas). The dotted lines represent survival of normal people of comparable age and sex. (Woolner LB, Beahrs OH, Black BM, McConahey WM, Keating FR. Thyroid carcinoma: general considerations and follow-up data on 1181 cases. In: Young S, Inman DR, eds. Thyroid neoplasia. New York, Academic Press, 1968:74)

patients with papillary cancer, Simpson and coworkers[127] noted 20-year cause-specific survival rates of 90% in patients with intraglandular tumors compared with 65% in patients with extraglandular extension.

Death from papillary carcinoma is significantly less common in patients diagnosed before age 40 compared with patients over 40 (Fig. 31-9).[127,161] A combination of extrathyroid extension and age greater than 40 carries a poor prognosis.[160]

For patients who do not undergo elective lymph node dissections, the reported failure rate in the neck is less than would be predicted from the incidence of subclinical metastases in patients who have undergone such operations.[33,34,46,66,80,96] The same is true of failure in the contralateral thyroid lobe after less than total thyroidectomy. Although failures in the retained lobe have sometimes been noted as long as 10 years or more after surgery,[111] the number of reported failures is less than the incidence of bilaterality noted in subserially sectioned total thyroidectomy specimens.[33,34] After conservative operations (eg, ipsilateral total and contralateral subtotal lobectomy combined with limited neck surgery), 10% to 20% of patients required reoperation for nodal or primary recurrent disease;[35,160] the frequency increased with primary size and extent. The salvage rate is high unless the soft tissues of the neck are involved by recurrent cancer.[34,82] Occasional patients must undergo a third, fourth, or even fifth operation.[160]

Asphyxia due to locally uncontrolled cancer is the immediate cause of death in the majority of patients who die of papillary carcinoma.[39,131] Distant metastasis alone as a cause of death occurred in only 9 (13%) of 70 patients who died of papillary carcinoma at Memorial Sloan-Kettering Hospital.[140] Occasional patients may live 20 or more years in a relatively asymptomatic state despite pulmonary metastases.[46]

Cause-specific survival rates from 13 Canadian centers for patients with papillary carcinoma who had "no residual disease" after surgery are shown in Figure 31-10[128] according to the type of adjuvant therapy administered. The local control results are summarized for the same treatment groups in Table 31-3. Neither adjunctive radioiodine nor external-beam irradiation improved local control or survival rates compared with surgery and thyroid hormone suppression.

A similar analysis for patients with microscopic residual disease (ie, positive surgical margins or tumor within 2 mm of the margin) is shown in Figure 31-11.[128] Approximately 80% of the patients had extraglandular tumor extension.[127] Local control results are summarized in Table 31-3. Adjuvant radioiodine therapy, external-beam irradiation, or both significantly improved both cause-specific survival and local control compared with surgery with or without thyroid hormone suppression.

Follicular Carcinoma

Survival of patients with follicular carcinoma correlates with the degree of histologic invasiveness (Fig. 31-12). With minimal or slight capsular invasion, 3 of 104 patients died of cancer.[161] Patients with more invasive lesions do poorly, with frequent local and distant failure, and most eventually die of cancer; many of the deaths

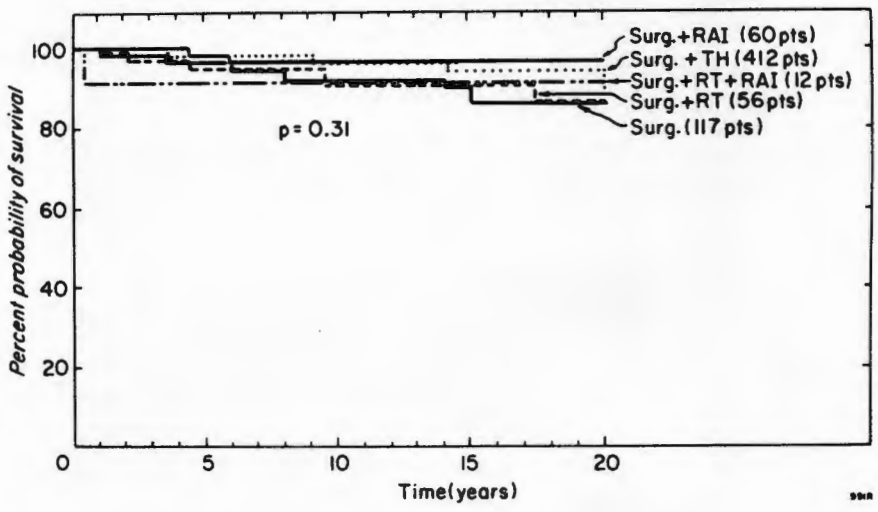

Figure 31-10. Cause-specific survival for patients with papillary carcinoma and "no residual disease" after surgery according to the type of adjuvant treatment administered (TH, thyroid hormone; RAI, radioiodine; RT, external-beam irradiation). From the National Thyroid Cancer Treatment Cooperative Study Group of Canada. (Simpson WJ, Panzarella T, Carruthers JS, Gospodarowicz MK, Sutcliffe SB. Papillary and follicular thyroid cancer: impact of treatment in 1578 patients. Int J Radiat Oncol Biol Phys 1988;14:1066)

TABLE 31-3. Local Control (4 to 24 Years of Follow-Up) According to Type of Adjuvant Treatment and Disease Status After Grossly Total Excision

Treatment	Papillary Carcinoma		Follicular Carcinoma	
	No Residual Disease	Microscopic Residual	No Residual Disease	Microscopic Residual
Surgery plus thyroid hormone	535 (86%)	38 (26%)	209 (85%)	21 (38%)
Surgery plus external-beam irradiation	56 (86%)	52 (90%)	21 (90%)	15 (53%)
Surgery plus radioiodine	61 (90%)	39 (82%)	57 (86%)	13 (77%)
Surgery plus external-beam irradiation plus radioiodine	12 (100%)	43 (86%)	10 (90%)	23 (70%)

Note: National Thyroid Treatment Cooperative Study Group, Canada.
(Modified from Simpson WJ, Panzarella T, Carruthers JS, Gospodarowicz MK, Sutcliffe SB. Papillary and follicular thyroid cancer: impact of treatment in 1578 patients. Int J Radiat Oncol Biol Phys 1988;14:1065)

occur after 5 years.[34,161] Patients over age 40 tend to have more invasive lesions and fare less well than those under age 40.[21,34,47]

In Simpson and McKinney's[126] review of 502 patients with follicular carcinoma, the overall survival rate at 20 years was 45%; the cause-specific survival rate at 20 years was 59% (ie, approximately two thirds of deaths were due to follicular carcinoma). In a separate review of 364 patients with follicular carcinoma, Simpson and coworkers[127] noted 20-year cause-specific survival rates of 80% in patients with intraglandular tumors compared with 50% in those with extraglandular extension.

Cause-specific survival rates from 13 Canadian centers for patients with "no residual disease" after surgery are shown in Figure 31-13[128] according to type of adjuvant therapy administered. The local control results for the same treatment groups are summarized in Table 31-3. Surgery plus thyroid hormone suppression was adequate in most situations.

A similar analysis for patients with microscopic residual disease (ie, positive margins or tumor within 2 mm of the margin) is shown in Figure 31-14.[128] Most patients had extraglandular extension.[127] Local control results are summarized in Table 31-3. Radioiodine with or without external-beam irradiation produced the highest rates of cause-specific survival and local control.

Hürthle cell tumors are generally more aggressive than papillary or follicular carcinomas.[54,116] The 10-year survival rate after surgery is approximately 60%[54,141] with most deaths being cancer-related.[116]

Medullary Carcinoma

In a review of 91 patients from 13 Canadian centers, Simpson and McKinney[126] noted 10-year overall and cause-specific survival rates of 56% and 70%, respectively. The majority of deaths were due to cancer.[114] Survival correlates best with nodal status. At the Mayo Clinic, 10-year survival in 74 patients with positive nodes was approximately one half that of 65 patients with negative nodes (Fig. 31-15).[26] After resection in 128

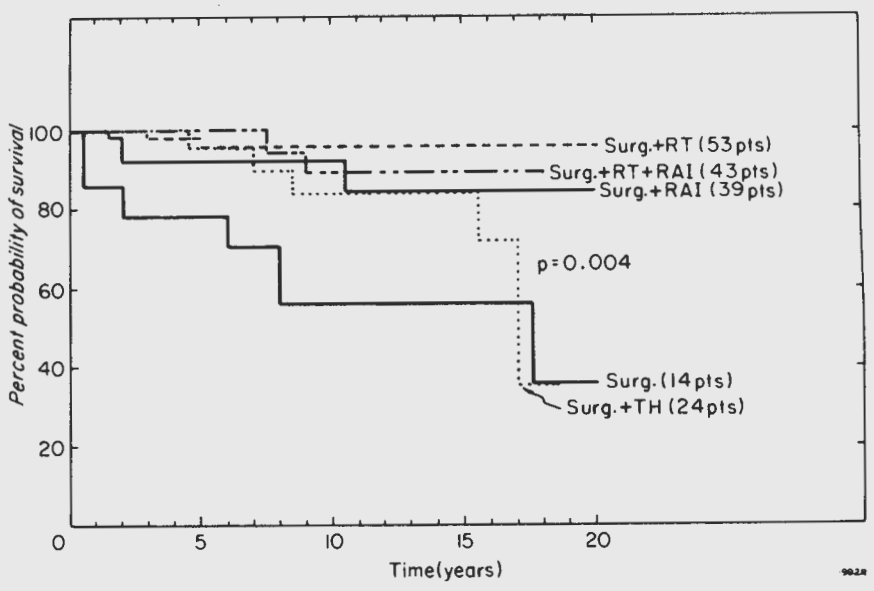

Figure 31-11. Cause-specific survival for patients with papillary carcinoma and "microscopic residual disease" after surgery according to the type of adjuvant treatment administered (TH, thyroid hormone; RAI, radioiodine; RT, external-beam irradiation). From the National Thyroid Cancer Treatment Cooperative Study Group of Canada. (Simpson WJ, Panzarella T, Carruthers JS, Gospodarowicz MK, Sutcliffe SB. Papillary and follicular thyroid cancer: impact of treatment in 1578 patients. Int J Radiat Oncol Biol Phys 1988;14:1066)

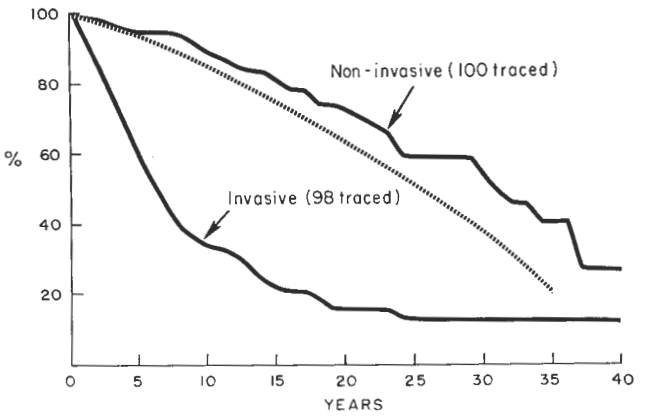

Figure 31-12. Survival after treatment of 198 traced patients with follicular carcinoma of thyroid gland (Mayo Clinic, 1926–1960). Noninvasive cases are those with slight or equivocal capsular invasion, and invasive cases are those with moderate to marked invasion, including recurrent or inoperable tumors. The dotted line represents survival of normal people of comparable age and sex. The 5-, 10-, and 15-year survival rates are all similar to those reported by Hirabayashi and Lindsay[63] at the University of California, San Francisco, for their localized and invasive subgroups. (Woolner LB, Beahrs OH, Black BM, McConahey WM, Keating FR. Thyroid carcinoma: general considerations and follow-up data on 1181 cases. In: Young S, Inman DR, eds. Thyroid neoplasia. New York, Academic Press, 1968:66)

patients at the Mayo Clinic, tumor recurrence was noted in almost two thirds of patients with positive nodes versus about 10% of those with negative nodes; 36 of 44 recurrences (82%) were local or regional, which is in general agreement with the pattern of failure observed at the M.D. Anderson Hospital.[62] In addition to the 44 patients with clinical recurrence, 12 others had persistently elevated plasma calcitonin levels. In Tubiana's[145] series, some patients with persistently elevated calcitonin levels remained free of clinical relapse after 5 to 10 years of observation, presumably because of dormancy or slow growth rate.

In the Institut Gustave-Roussy series, 62 patients without evidence of distant metastases were treated between 1932 and 1979. Fifty-six patients underwent partial or total thyroidectomy, with the addition of external-beam irradiation in 29. The irradiated group had a greater proportion of patients with involved lymph nodes (86% versus 59%, *P* less than .05) and more frequently had histologically incomplete resections (44% versus 12%). Nevertheless, survival was higher through 25 years of follow-up in the postoperatively irradiated group (Fig. 31-16).[114]

All six patients at Institut Gustave-Roussy who had inoperable, extensive neck tumors were treated by external-beam irradiation alone. One patient remained free of disease at 4 years. The other five developed recurrent disease, although four responded initially with greater than 50% tumor shrinkage. Three of the five lived 4 to 10 years.[114] Thirteen other patients at Institut Gustave-Roussy had distant metastases at diagnosis; the 5-year survival rate was 25%.[114]

Because of the significant effect of nodal status on curability, early detection of familial cases by annual calcitonin screening of family members is indicated. Patients with MEN IIB have poor survival rates.[97]

Anaplastic Carcinoma

In most series, approximately 90% of patients are dead within 1 year. Local, regional, and distant failures are all frequent. The only patients cured with any regularity have the unusual circumstance of disease confined to the gland and regional lymph nodes, without extension into the soft tissues of the neck.[1]

The initial enthusiasm for combination surgery, irradiation, and dactinomycin at the M.D. Anderson Hospital waned after the initial report of three of six patients cured;[109] the combined approach failed to produce a single long-term survivor in eight additional patients treated over the succeeding 6 years.[1]

Tallroth and coworkers[136] reported on four different treatment schemes used at the Karolinska Institute between 1971 and 1985. Eight patients between 1971 and 1973 received 3000 to 4000 cGy over 3 to 4 weeks plus concurrent intraarterial or intravenous methotrexate.

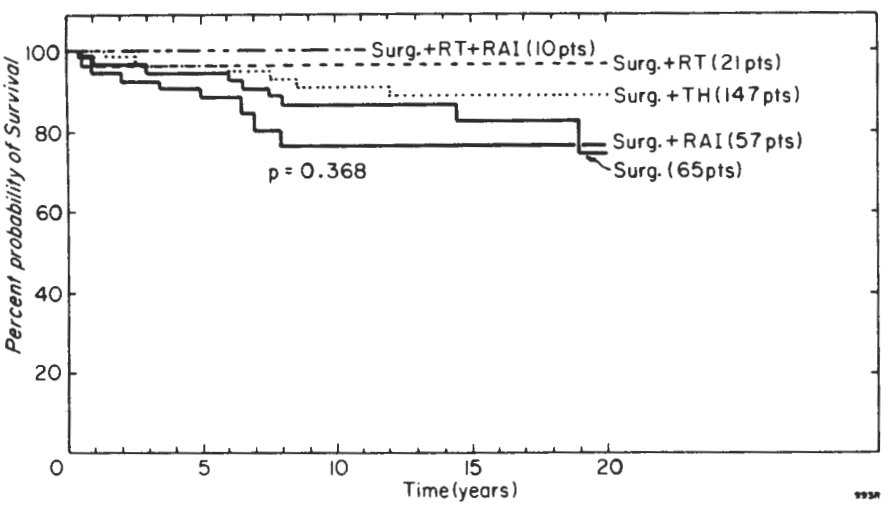

Figure 31-13. Cause-specific survival for patients with follicular carcinoma and "no residual disease" after surgery according to the type of adjuvant treatment administered (TH, thyroid hormone; RAI, radioiodine; RT, external-beam irradiation). From the National Thyroid Cancer Treatment Cooperation Study Group of Canada. (Simpson WJ, Panzarella T, Carruthers JS, Gospodarowicz MK, Sutcliffe SB. Papillary and follicular thyroid cancer: impact of treatment in 1578 patients. Int J Radiat Oncol Biol Phys 1988;14:1066)

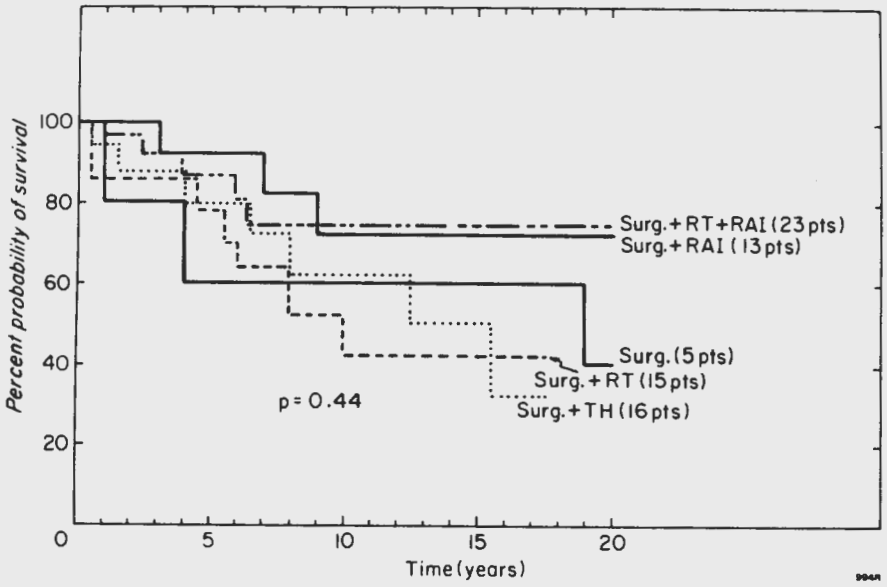

Figure 31-14. Cause-specific survival for patients with follicular carcinoma and "microscopic residual disease" after surgery according to the type of adjuvant treatment administered (TH, thyroid hormone; RAI, radioiodine; RT, external-beam irradiation). From the National Thyroid Cancer Treatment Cooperative Study Group of Canada. (Simpson WJ, Panzarella T, Carruthers JS, Gospodarowicz MK, Sutcliffe SB. Papillary and follicular thyroid cancer: impact of treatment in 1578 patients. Int J Radiat Oncol Biol Phys 1988;14:1067)

Seven experienced greater than 50% reduction in tumor size, but none was cured. Severe toxicity was experienced by all eight patients.

From 1973 to 1975, nine patients received 3000 to 4000 cGy over 3 to 4 weeks with concurrent bleomycin, cyclophosphamide, and 5-fluorouracil (BCF). All patients experienced treatment complications, but none were severe. Tumor regressions were transient. One of the nine patients, the only one who underwent surgery, was cured (12+ years). After that experience, surgery was considered for all patients.

From 1975 to 1983, 20 patients received twice-a-day radiotherapy (100 cGy per fraction) to 3000 cGy and BCF chemotherapy, preoperatively, followed by surgery after 2 to 3 weeks whenever feasible, then an additional 1600 cGy (100 cGy twice a day) plus concurrent chemotherapy. It was possible to perform surgery in 12 patients. Additional chemotherapy (cyclophosphamide and 5-fluorouracil) was continued after irradiation. Fifteen of the 20 patients achieved greater than 50% tumor reduction. Three patients remained tumor-free at 3½, 6½, and 11 years; all three were among the 12 patients who underwent thyroidectomy.

In 1984, BCF was replaced with doxorubicin. Although the toxicity was reduced, the treatment results were inferior to those achieved with BCF.

Kim and Leeper[72] reported on 19 patients with anaplastic carcinoma at Memorial Sloan-Kettering who received twice-a-day radiotherapy (160 cGy twice-a-day, 3 days per week to 5760 cGy in 6 weeks) and concurrent low-dose, once-weekly doxorubicin (10 mg/m^2). Ten patients underwent subtotal thyroidectomy and modified neck dissection before irradiation; the rest had biopsy only. Actuarial 2-year local control was 68%. Fifteen of 19 patients died of distant metastases. The only patients who survived beyond 1 year had resectable disease with minimal residual disease after surgery.

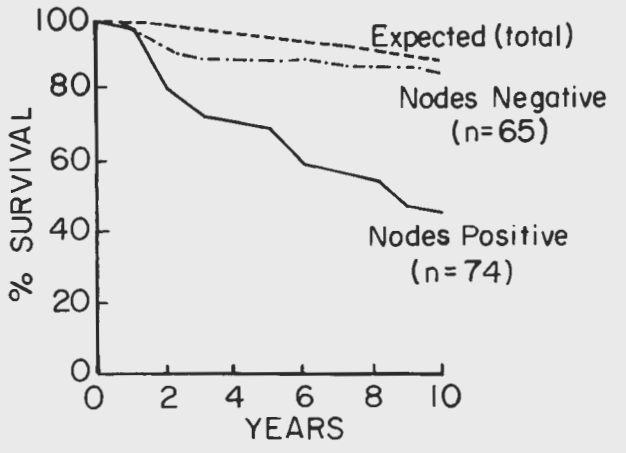

Figure 31-15. Survival after treatment of 139 patients with medullary carcinoma of the thyroid gland (Mayo Clinic, 1926–1973) according to nodal status at the time of operation. The dashed line represents survival of normal people of comparable age and sex. (Redrawn from Chong GC, Beahrs OH, Sizemore GW, Woolner LH. Medullary carcinoma of the thyroid gland. Cancer 1975;35:701)

COMPLICATIONS OF TREATMENT

The operative mortality rate from thyroidectomy is about 0.1%.[7] The most serious immediate postoperative hazard is hemorrhage. Blood tends to be trapped in the midline of the neck and may lead to rapid airway collapse. In severe cases, the wound must be opened immediately. After the obstruction has been relieved, the patient is transferred back to the operating room, the bleeding is controlled, and a tracheostomy is created if necessary. Severe hemorrhage occurred after only 1 of 574 consecutive thyroidectomies at the Mayo Clinic.[6]

Mild, asymptomatic hypocalcemia occurs after thyroidectomy in about 25% of patients, is maximal 48 to 72 hours postoperatively, then disappears within 1 week.[6,155] Such transient drops in serum calcium are believed to be secondary to trauma to the parathyroid glands or to their blood supply. The sooner after surgery the drop occurs and the longer it persists, the less likely

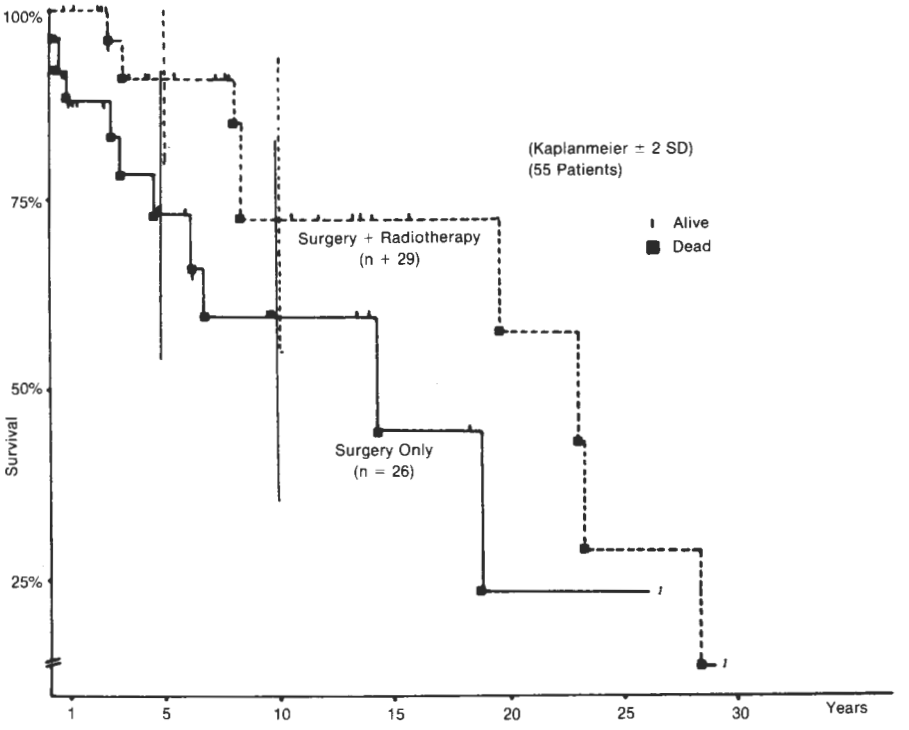

Figure 31-16. Actuarial survival curves (±2 SD [Kaplan and Meier][71]) according to treatment of patients with medullary thyroid carcinoma (Institut Gustave-Roussy, 1932–1979). Dotted line = surgery and local radiotherapy (n = 29); solid line = surgery alone (n = 26). (Rougier P, Parmentier C, Laplanche A, Lefevre M, Travagli JP, Caillou B, Schlumberger M, Lacour J, Tubiana M. Medullary thyroid carcinoma: prognostic factors and treatment. Int J Radiat Oncol Biol Phys 1983;9:165)

is recovery, because all parathyroid tissue may have been removed or its vascular supply so compromised that it ceases to function.

The risk of permanent hypoparathyroidism relates mainly to the extent of surgery, as dictated by the extent of disease, and to the experience and skill of the surgeon. There is little risk if only a single thyroid lobe is removed or if one leaves a small remnant of one lobe behind and ablates the remaining thyroid tissue with ^{131}I. In cases in which total thyroidectomy is necessary, permanent hypoparathyroidism is reported in 15% to 20% of patients.[36,49,74] If parathyroid tissue is visualized at operation, it should be protected. If it appears that the parathyroid glands are going to be jeopardized, one of the glands may be identified histologically and transplanted into the sternocleidomastoid muscle. After an extensive operation, signs of hypoparathyroidism are sought and the serum calcium level is checked daily; replacement therapy is begun only in the presence of hypocalcemic signs.[40] Permanent hypoparathyroidism requires indefinite calcium replacement; vitamin D is also usually given.

Inadvertent section of one recurrent laryngeal nerve occurred in about 1% of patients operated on at the Mayo Clinic. It is advisable to control bleeding during operation with finger pressure until normal structures can be clearly identified. Indiscriminate and blind clamping in a pool of blood is liable to result in nerve injury. At no time should sharp dissection or clamping be done in the region of the nerve unless it is clearly in sight.[6] The risk of nerve damage is greater in patients who undergo reexploration because of edema and inflammatory reaction (during the weeks immediately after surgery) and fibrosis (months to years after operation).[6,7] Bilateral recurrent laryngeal nerve injury is extremely rare and usually necessitates permanent tracheostomy or a secondary procedure such as arytenoidectomy. Transient nerve injuries, due to stretching or trauma, usually resolve within a few months.[6]

Damage to the external branch of the superior laryngeal nerve results in voice fatigue. Horner's syndrome is rare, but may occur secondary to injury to the cervical sympathetic chain at the time of ligation of the inferior thyroid artery.[40]

A rare complication is pneumothorax, secondary to injury to the lung apex.[6]

Bone marrow depression may occur after large single doses or multiple small doses of radioiodine; it is usually transient and does not require treatment.[30] The risk of developing acute leukemia or aplastic anemia is small and related to total cumulative dose.[110,125,147] The total body dose from ^{131}I is approximately 0.25 to 0.50 cGy per millicurie administered.[111,118] Patients with multiple fine, diffuse lung metastases are at risk of developing radiation-induced pneumonitis or pulmonary fibrosis from ^{131}I therapy.[46] In two fatal cases of radiation pneumonitis reported at Memorial Sloan-Kettering Hospital, dyspnea on exertion first appeared 2 months after large single doses of ^{131}I; severe respiratory distress and cyanosis were present by about 3 months, and death occurred shortly thereafter.[102] Transformation of well-differentiated to anaplastic carcinoma[35] is seen in a small percentage of patients, whether they receive radioiodine or not;[1,94] there are no data to suggest that the incidence is increased by radioiodine. Long-term follow-up of patients (aged 6 to 20) treated for thyroid cancer with ^{131}I (total dose 80 to 690 mCi; mean 196 mCi) has disclosed no apparent increase in occurrence of infertility or birth defects compared with the general population.[118] Of 33 married patients (13 men, 20 women) on whom follow-up was available 14 to 25 years after treatment, there were 71 live births in 29 families. Four patients (12%) were apparently infertile. There was one major congenital (cardiac) anomaly (1%). The authors estimated go-

nadal doses to be approximately 0.1 cGy per millicurie administered.

In the rare patient with hyperthyroidism secondary to functioning metastatic thyroid carcinoma, it is important to establish a euthyroid state by administering an antithyroid agent before radioiodine therapy; failure to do so may result in thyroid storm and death.[24]

Complications of external-beam irradiation are discussed in Chapter 13. Tissues at risk include the spinal cord, larynx, trachea, esophagus, subcutaneous tissues, and brachial plexus.

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32

PEDIATRIC TUMORS OF THE HEAD AND NECK

ROBERT B. MARCUS, JR., J. CHRISTOPHER POST, AND ANTHONY A. MANCUSO

Excluding accidents, malignant neoplasms are the leading cause of death for all pediatric age groups once the neonatal period is passed. Still, pediatric cancer is a rare disease, and the National Cancer Institute's Program Surveillance, Epidemiology, and End Results (SEER) showed an incidence in children younger than the age of 15 of only 129.5 cases per year per million white children and 104.1 cases per million black children.[202] This means that over the first 15 years of life, about 2 of every 1000 children will develop cancer. The incidence has been stable over the past 20 years, although the death rate has decreased, particularly from 1965 through 1975.[200]

About 10% of pediatric neoplasms occur in the head and neck. The most common histologic subtypes and their estimated frequency are shown in Table 32-1.[17,82,155,182]

In general, the treatment strategies applicable to cancer of the head and neck in children are similar to those used for tumors of similar histology presenting elsewhere in the body. The occurrence in the head and neck, however, does make the surgical approach more difficult for many of these lesions, particularly the sarcomas. Because of the many critical developing structures in the head and neck, the radiotherapeutic management may also be more difficult. A team approach is necessary, and many tumors that were previously fatal are now cured with an aggressive, well-planned therapeutic attack. Because of the rarity of the tumors, they are best treated in centers specializing in pediatric cancer. Retinoblastoma is an ophthalmologic problem and it will not be discussed in this text. Lymphomas and carcinomas of the thyroid, skin, nasopharynx, and major and minor salivary glands are discussed in specific chapters, as is juvenile angiofibroma. Discussion of a few benign lesions is included in this chapter.

MALIGNANT TUMORS

Soft Tissue Sarcomas

Rhabdomyosarcoma

Rhabdomyosarcomas are tumors of the skeletal muscle and comprise the overwhelming majority of soft tissue sarcomas in children. The incidence is about 4.5 per million children per year younger than the age of 15, representing about 3.5% of all malignant neoplasms in children. According to the First and Second Intergroup Rhabdomyosarcoma Studies (IRS-I and IRS-II), 35% of pediatric rhabdomyosarcomas occur in the head and neck.[139]

PATHOLOGY. Rhabdomyosarcomas are now divided into four histologic types: embryonal, alveolar, botryoid, and pleomorphic. Embryonal and botryoid subtypes account for 91% of primary lesions of the head and neck, with only 2% being alveolar. Three additional small cell mesenchymal sarcomas that behave similar to rhabdomyosarcoma have been described by the pathology committee of the IRS: extraosseous Ewing's sarcoma; small round cell tumor, type indeterminate; and sarcoma, not classified.

PATTERNS OF SPREAD

Local Spread. The areas of local spread include the following:

Orbit. About 70% of orbital rhabdomyosarcomas start in the tissues posterior to the globe. Another 20% arise in the eyelid and 5% occur in the conjunctiva.[86] The bony orbit, although thin, still produces a barrier for growth of tumor in all directions ex-

TABLE 32-1. Incidence of Malignant Solid Tumors of the Head and Neck* in Children

Tumor	No. of Cases	Percentage
Lymphoma	352	42.6
Rhabdomyosarcoma	237	28.7
Other soft tissue sarcomas	60	7.3
Fibrosarcoma	40	4.8
Squamous cell carcinoma	53	6.4
Thyroid carcinoma	36	4.4
Neuroblastoma	27	3.3
Mucoepidermoid carcinoma	10	1.2
Bone tumors	10	1.2
Ewing's sarcoma	7	0.8
Osteosarcoma	3	0.4
Melanoma	7	0.8
Other	34	4.1
Total	826	100.0

* Excluding central nervous system tumors and retinoblastoma.
Compiled from references 17, 82, 155, and 182.

cept anteriorly (Fig. 32-1).[115] The tumor can, however, grow posteriorly to involve the extraocular muscles and rarely may extend through the orbital foramen or supraorbital fissure into the central nervous system. If allowed to progress, these tumors will eventually violate the medial wall of the orbit and extend into the nasal cavity or ethmoid sinuses.

Nasopharynx and paranasal sinuses. Lesions starting in the nasopharynx or paranasal sinuses are usually rapidly growing tumors and quickly invade neighboring structures (Figs. 32-2 and 32-3). In one series, only 4 of 20 primary rhabdomyosarcomas of the nasopharynx remained confined to the nasopharynx.[23]

Middle ear. Middle ear lesions appear to have two different sites of origin: the regions of the mastoid and petrosal bones.[22] Mastoid lesions are the most common (Fig. 32-4). They often spread along the internal auditory canal and then to the prepontine leptomeninges. In doing so, they usually involve the facial nerve. It has been shown that the facial canal is a vulnerable area to tumors that "when penetrated provides a channel for direct extension into the auditory meatus and posterior fossa" (see Fig. 32-4*B*).[134] From there, the development of the hemibase syndrome often occurs (involvement of multiple cranial nerves on one side by an extra-axial process).

Petrous lesions pursue a different course, probably starting in the region of the eustachian tube, tensor tympani muscle, or carotid canal. Spread occurs through the petrous bone with early abducens nerve paralysis resulting from cavernous sinus involvement in the region of Dorello's canal. Further extension into the carotid canal involves the sympathetic nerves (causing Horner's syndrome) and the trigeminal nerve as it crosses the petrous ridge. Oddly enough, even in large tumors, invasion of the labyrinth is rare (see Fig. 32-4*B*).

Larynx. The rare laryngeal primary lesions appear to arise from diverse parts of the larynx and pyriform sinus.[24]

Other head and neck sites. The other primary sites are less common, but, in general, rhabdomyosarcomas arising in the oral cavity, oropharynx, cheek and masseter, parotid, scalp, and neck spread locally like primary carcinomas in these sites. They grow very rapidly and can reach a large size.[195]

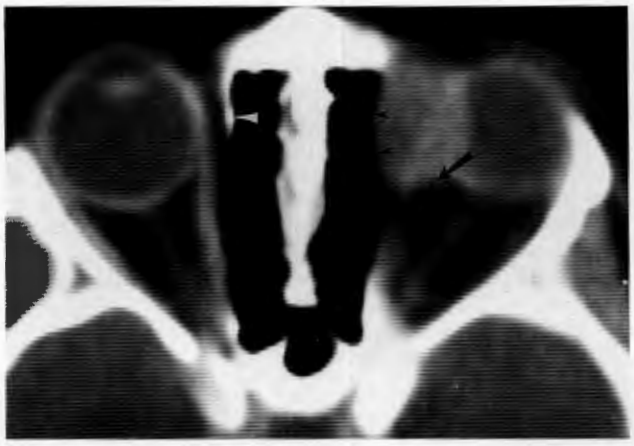

Figure 32-1. An orbital rhabdomyosarcoma involving the extraconal orbital fat and muscle cone at the medial rectus insertion and extending intraconally (*arrow*). The medial wall of the orbit is eroded (*arrowheads*) compared with the normal side (*white arrowhead*).

Meningeal Involvement by Parameningeal Primary Lesions. In addition to the routes of spread previously described, evidence indicates that lesions in the middle ear and mastoid, infratemporal fossa and parapharyngeal region, nasopharynx and nasal cavity, and paranasal sinuses (the parameningeal sites) have an increased risk of meningeal extension.

Apparently, local invasion into the base of the skull is followed by extension to the leptomeninges first, then to the brain itself by way of the Virchow–Robin spaces.[105] Ultimately, the entire subarachnoid space of the entire neural axis may be involved.

Interestingly enough, meningeal extension by orbital lesions is rare.

Lymph Node Spread. Clinically positive neck nodes at diagnosis are unusual in head and neck rhabdomyosarcoma, as is microscopic involvement found by an elective neck dissection.[103]

In IRS-I and IRS-II, no patients with orbital primary lesions presented with clinically positive neck nodes, while 8% of patients with other primary tumors had positive nodes.[102]

Metastasis Beyond the Clavicles. About 13% of patients with head and neck rhabdomyosarcomas present with distant metastases at the time of diagnosis, except for orbital primary lesions, which have a 4% incidence.[181]

The most common site of distant metastasis for primary lesions of the head and neck is the lung, followed by the bone marrow.[153]

CLINICAL PICTURE AND DISTRIBUTION.

Orbit. The most common presenting symptom in orbital lesions is proptosis, which is often of rapid

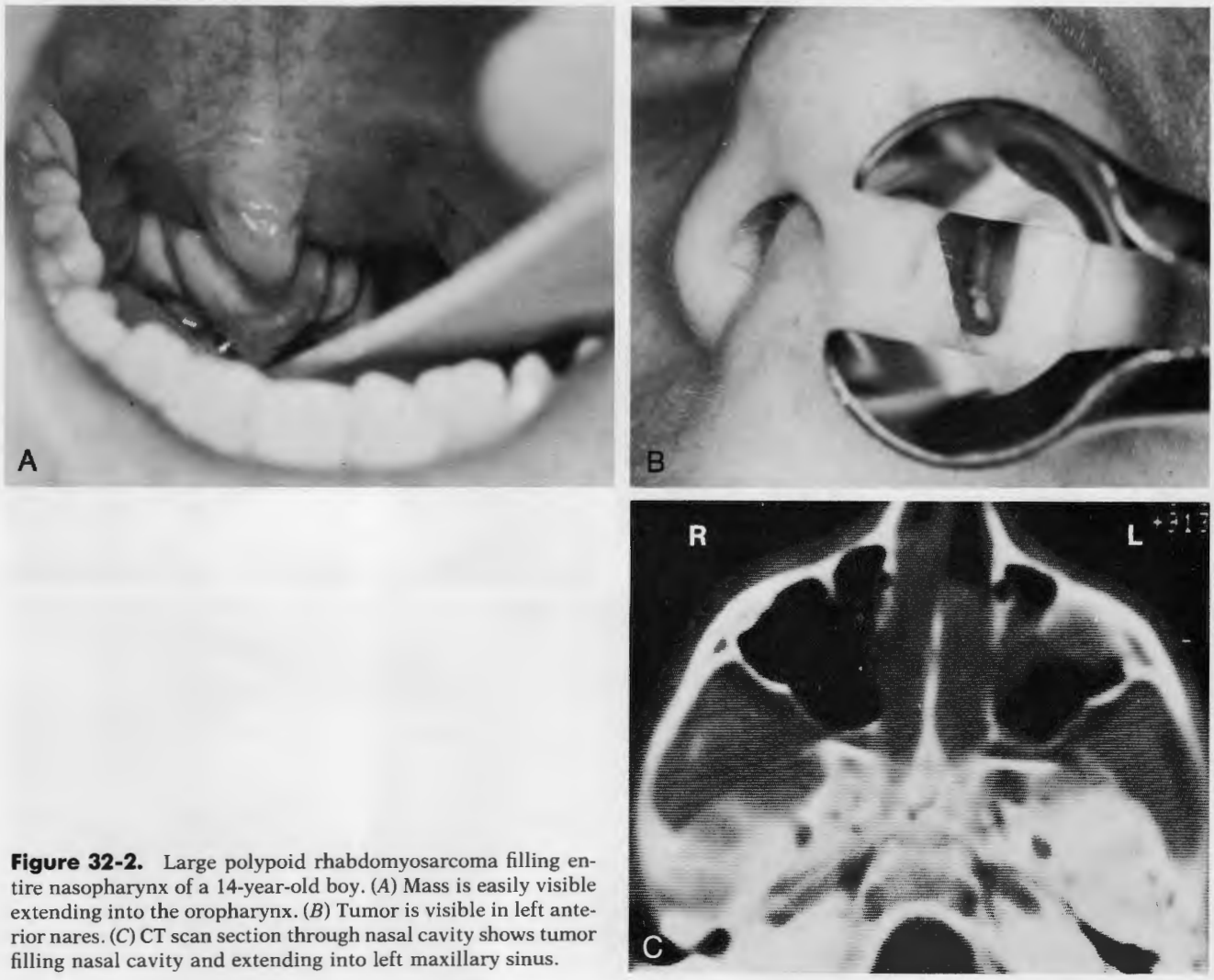

Figure 32-2. Large polypoid rhabdomyosarcoma filling entire nasopharynx of a 14-year-old boy. (*A*) Mass is easily visible extending into the oropharynx. (*B*) Tumor is visible in left anterior nares. (*C*) CT scan section through nasal cavity shows tumor filling nasal cavity and extending into left maxillary sinus.

and alarming progression and accompanied by diplopia, drooping of the upper lid, and even a decrease in visual acuity or blindness (see Fig. 32-1). At this point, a discrete mass may be palpated in about one fourth of the patients. A few patients will complain of pain or tearing early in the course of the disease, and a few patients are diagnosed because of epistaxis, with the tumor having penetrated into the nasal cavity.[86]

Nasopharynx and paranasal sinuses. Patients with primary rhabdomyosarcomas of the nasopharynx and sinuses usually present with ear symptoms; fullness due to eustachian tube obstruction and tinnitus are the most common complaints. Nasal obstruction, epistaxis, dysphagia, and local pain are also common presenting symptoms. Tumor in the parapharyngeal space may cause cranial nerve deficits (see Figs. 32-2 and 32-3).

Middle ear. With primary lesions in the middle ear, there is almost always a painless discharge as the first symptom. A small mass may be noticed in the external auditory canal, and a diagnosis of otitis media is often made (see Fig. 32-4). In the past, preliminary roentgenographic evaluation produced a diagnosis of mastoiditis, with or without bone destruction. Imaging with computed tomography (CT) or magnetic resonance imaging (MRI) will help avoid delay in diagnosis. By the time the diagnosis is made, however, more advanced symptoms are usually present. Facial nerve palsy has been reported in as high as 88% of patients, while other cranial nerves were involved in 28%.[105] In addition, 28% of patients presented with a postauricular mass or swelling (see Fig. 32-4).

Oral cavity and oropharynx. Primary lesions in the oral cavity or oropharynx may cause pain, but since many occur in young children (they have even been reported at birth), symptoms such as dyspnea, dysphagia, cough, or abnormal phonation are noted. Trauma to the tumor from sucking or swallowing may cause bleeding, and blood may be found on the bed of an infant.[110]

Larynx. Laryngeal lesions are extremely rare. When the patient is an infant, symptoms of croup or "noisy breathing" have been reported.[7] The onset of dyspnea may be rapid.

Other head and neck sites. Rhabdomyosarcomas of the scalp, cheek, parotid, temporal region, and neck usually present as an asymptomatic, rapidly growing mass.

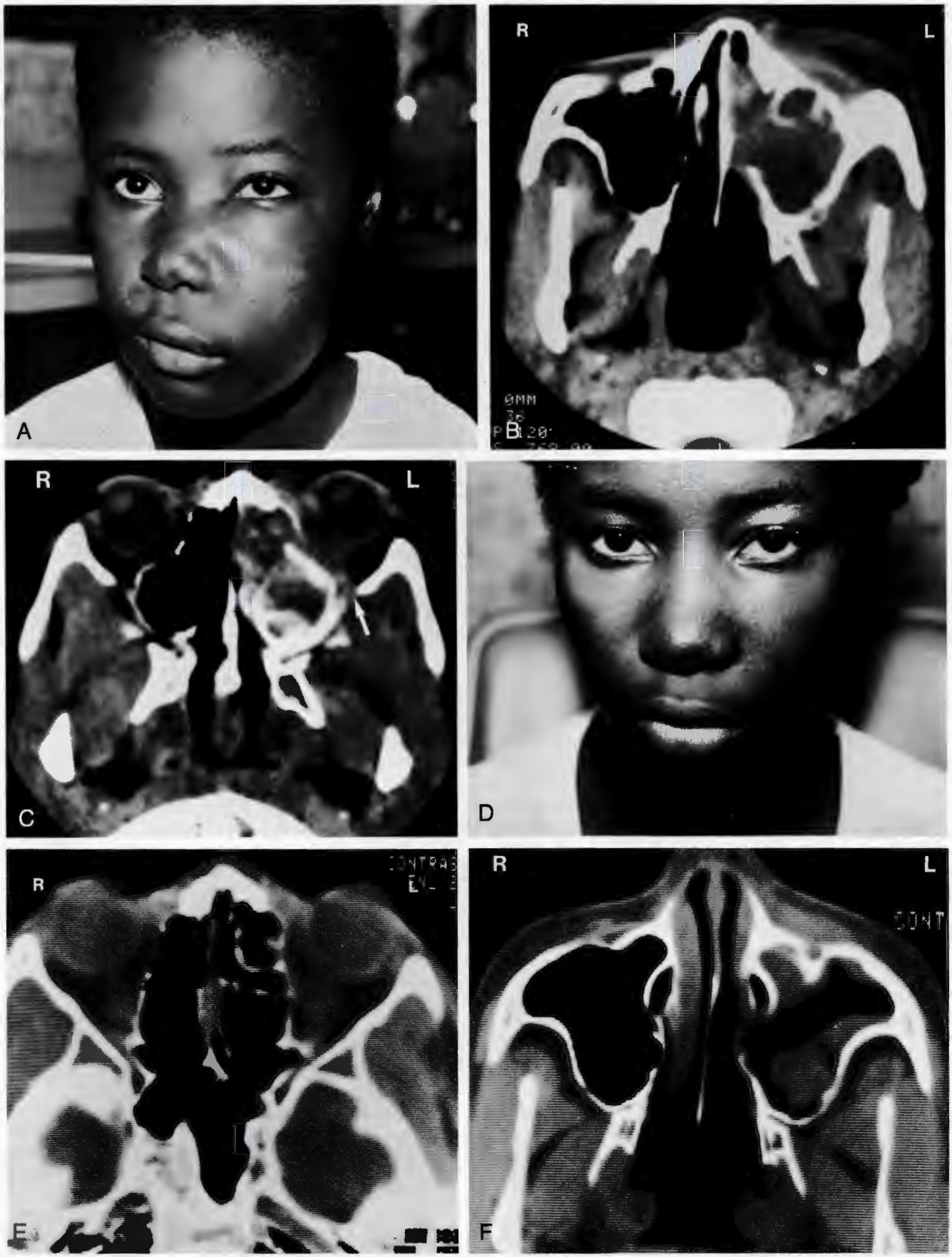

Figure 32-3.

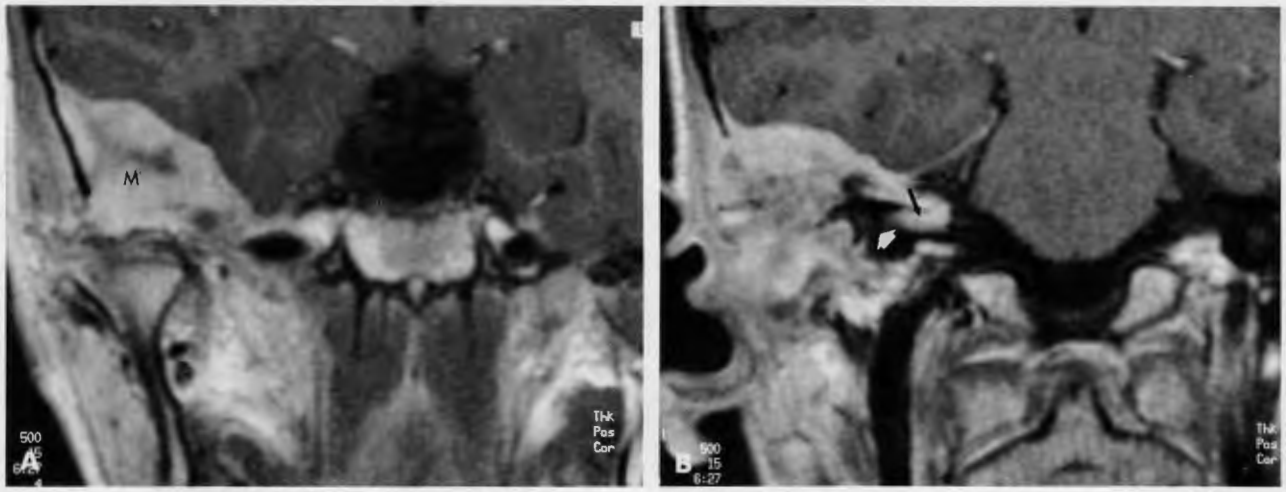

Figure 32-4. A 3-year-old girl presented with a mass in the periauricular region subsequently proven to be a temporal bone rhabdomyosarcoma of mastoid origin. (*A*) Coronal, T1-weighted, contrast-enhanced MRI shows a partially necrotic mass (M) involving the mastoid portion of the temporal bone and extending intracranially, although it remains extradural. This is a good example of bulky parameningeal disease. (*B*) Coronal MRI section posterior to that in *B* shows tumor spreading within the internal auditory canal (*black arrow*), probaby reaching it through the facial canal. Note the sparing of the bony labyrinth (*white arrow*). This patient is at high risk for central nervous system dissemination because of this spread to the internal auditory canal.

STAGING. The IRS staging system is the most commonly used in the United States. For IRS-I, IRS-II, and IRS-III the grouping system in Table 32-2 has been used. A problem may occur, however, if one institution chooses a more radical surgical approach than another, thus changing the IRS grouping of the lesion. For this reason, a new staging system is to be evaluated prospectively in the IRS-IV studies.[1,43,101,124]

DIAGNOSTIC EVALUATION. The evaluation of a patient with rhabdomyosarcoma is directed at determining both the extent of local disease as well as the possible presence of distant metastases. As a minimum, after a history and physical examination, a complete blood cell count, platelet count, differential count, liver function studies, renal function studies, and urinalysis should all be done. The lungs should be evaluated with CT of the thorax. A bone scan and bone marrow aspiration and biopsy are also necessary.

To evaluate the local extent of primary tumor, conventional roentgenograms should be done, followed by contrast-enhanced CT, MRI, or both (see Figs. 32-1 through 32-4).

In addition, for parameningeal lesions the central nervous system must be evaluated. The MRI of the primary site can be extended to cover the entire brain and must be done with the injection of paramagnetic contrast medium. Since even those patients with no roentgenographic evidence of invasion of the base of the skull or overt central nervous system disease may still have involvement of the central nervous system, a spinal tap is advised for the parameningeal primary lesions, and frankly malignant cells will sometimes be found.

SELECTION OF TREATMENT MODALITIES. Surgery is the local treatment of choice for small lesions (eg, those of the tongue, buccal mucosa, scalp, parotid gland, and neck) that can be removed with minimal cosmetic or functional deformity. Most lesions of the head and neck, however, are difficult to resect because of the anatomic location, and radiation therapy is the treatment of choice. Orbital lesions, even though operable, have a high rate of control with radiation therapy, and vision may be preserved in a few cases.

All patients with head and neck rhabdomyosarcomas should receive systemic chemotherapy. With small re-

◄ **Figure 32-3.** (*A*) A 14-year-old girl had a 3-week history of swelling in the left side of the face and a 1-week history of diplopia. Physical examination revealed a large palpable tumor mass beneath the left cheek and extending into the left alveolar ridge. (*B*) CT scan revealed involvement of the left maxillary sinus, the orbit, the nasal cavity, the infratemporal fossa, and the soft tissues of the premaxilla. (*C*) Tumor involves the left ethmoid sinus and the medial portion of the left orbit and extends through the inferior orbital fissure (*arrow*) to the infratemporal fossa. Biopsy revealed embryonal rhabdomyosarcoma. Chemotherapy consisting of vincristine, doxorubicin HCl (Adriamycin), cyclophosphamide, and dactinomycin was begun. (*D*) After 6 weeks of chemotherapy, just before the start of radiation therapy, there was no evidence of tumor by physical examination. (*E*) Repeat CT scan showed no definite residual tumor in the left orbit. (*F*) There was residual tumor in the left maxillary sinus and in the premaxillary soft tissues. The fascial planes in the infratemporal fossa behind the left maxillary sinus returned to normal. Five years after completion of therapy, the patient remained clinically and radiographically free of disease.

TABLE 32-2. Intergroup Rhabdomyosarcoma Study Grouping System

Group	Description
I	Localized disease, completely resected; regional nodes not involved
IIA	Grossly resected tumor with microscopic residual disease; no evidence of regional node involvement
IIB	Regional disease (extension into adjacent organ or regional nodes), completely resected
IIC	Regional disease with involved nodes, grossly resected, but with evidence of microscopic residual
III	Gross residual disease after surgery
IV	Metastatic disease at diagnosis

Data from Maurer and coworkers.[124]

sectable primary lesions, good results are obtained with postoperative chemotherapy. With larger lesions, several cycles of chemotherapy should be given initially to decrease the amount of disease before local treatment (see Fig. 32-3). If irradiation is given (to be started on week 9 in the present intergroup study, IRS-IV), chemotherapy should continue throughout irradiation and for 12 to 18 months after its initiation. A few patients may need combined surgery and radiation therapy at the primary site; induction chemotherapy should be given first, followed by irradiation, then excision of residual disease. Some authors have recommended a different approach: chemotherapy, then surgery, followed by radiation therapy last.[48] Both approaches work for some lesions that are not resectable at diagnosis.

The clinically negative neck requires no treatment beyond chemotherapy and careful observation.[124] Patients with a clinically positive neck who have resection of their primary lesion are probably best treated with a neck dissection. Even a young child whose primary lesion is irradiated may have a better end result with a neck dissection rather than irradiation of bulky adenopathy. It may be preferable to wait until after initial chemotherapy before proceeding with the neck dissection. For multiple positive nodes, both a neck dissection and irradiation may be necessary.

SURGERY. The basic principle of wide resection of the primary tumor including surrounding normal tissue is a difficult concept to apply without producing considerable morbidity or deformity. For parameningeal rhabdomyosarcomas, biopsy is probably the best the surgeon can obtain, leaving most of the treatment to the radiation therapist and chemotherapist. For operable lesions, the appropriate surgical procedures are described elsewhere in this book.

RADIATION THERAPY. The radiation treatment of head and neck sarcomas in children is one of the most difficult tasks in pediatric radiation therapy. The volume of tissue to be treated is usually large enough to include a number of sensitive structures, and the dose required for control is high enough to cause profound soft tissue side effects in the growing child. Therefore, careful treatment planning is necessary to minimize long-term side effects, particularly when concomitant chemotherapy is given. The natural tendency to minimize the volume of irradiation must be avoided, since it has been shown that an insufficient volume increases the rate of local recurrence.[188]

The techniques for each site are similar to those used for primary carcinomas and are presented in other chapters of this book. A few important guidelines are presented here.

- At a minimum, the tumor plus a 2-cm margin should be irradiated, but a margin of 3 cm is about the maximum one should attempt. There are too many vital structures in or near the field to treat larger margins.
- For many lesions, use of parallel opposed fields is not appropriate. Morbidity can be minimized by using wedged pairs or multiple fields.
- For sinus and nasopharynx lesions, adding an anterior field to the lateral ones can significantly decrease the dose to the temporomandibular joints, the parotid glands, and possibly to one or both eyes. The decrease is often enough to preserve function in these organs. (See Figs. 22-35 through 22-38 in Chapter 22.)
- The dose to the temporomandibular joints and parotid glands can be further reduced by using higher-energy x-rays for the lateral fields, which is possible if there are no clinically palpable lymph nodes. Care must be taken not to underdose the lateral extent of the tumor, since extensions into the temporal fossa or pterygoid space may bring the tumor close to the lateral surface of the head.
- For parameningeal lesions, the superior margin must be at least 2 cm above the base of the skull, even if no cranial nerves are involved and there is no radiologic evidence of invasion of the base of the skull.
- If cranial irradiation is to be used (ie, if the cerebrospinal fluid contains tumor cells), then the treatment of the primary tumor should be incorporated into the whole brain fields. The fields are reduced to treat just the primary site after 3000 cGy. The radiation therapy in this case should usually be given with induction chemotherapy, at the beginning of all treatment.

It appears from the scant data available that the best local control results for gross disease have been reported with doses from 5500 to 6000 cGy at 180 cGy per day, although the recent IRS protocols recommend use of a dose of 5040 cGy (Table 32-3).[9,29,85,188]

The shrinking fields technique can be used to decrease morbidity, with a field size reduction after 3500 to 4000 cGy. A dose of 3500 to 4000 cGy should be adequate for subclinical disease in the neck after positive nodes have been removed.[99,116,188] The usual doses for gross disease should be employed for clinically positive adenopathy. Although dose reductions have been recommended in the past for children younger than 6 years of age, similar doses are now used for all ages.

In an attempt to improve local control rates while keeping late effects acceptable, hyperfractionation is now being studied in IRS-IV with randomization between 5040 cGy at 180 cGy per day and 5940 cGy at 110 cGy twice a day.

CHEMOTHERAPY. Combination chemotherapy is now an integral part of the treatment of childhood rhabdomyosarcoma. Multiple drugs have been found to be effective, including dactinomycin (actinomycin D),[184]

TABLE 32-3. Pediatric Rhabdomyosarcoma: Local Control of Gross Disease According to Dose*

Series	Local Control of Gross Disease			
	<45 Gy	≥45 Gy, <50 Gy	≤50 Gy, <55 Gy	≥55 Gy
IRS-1[188]	<50 Gy: 50/56 (89%)		≥50 Gy: 99/115 (86%)	
Princess Margaret Hospital[9]†	0/2	5/8 (62%)	8/11 (73%)	4/4 (100%)
M. D. Anderson Hospital[29]‡	No data	No data	No data	23/27 (85%)
Memorial Sloan-Kettering Cancer Center[85]	11/22 (50%)	3/3	4/6 (67%)	11/12 (92%)

* Once-a-day fractionation, 160 to 200 cGy per day.
† Excludes patients who did not receive adjuvant chemotherapy.
‡ Parameningeal head and neck lesions only.

vincristine,[180] cyclophosphamide,[63] ifosfamide, and doxorubicin (Adriamycin).[59,149]

Most regimens use a combination of drugs.[73,85,124,152,179] The VAC regimen (vincristine, dactinomycin, and cyclophosphamide) has been the most widely used in the past, but regimens containing doxorubicin may be more effective. The IRS is presently also testing combinations of vincristine, doxorubicin, and ifosfamide as well as vincristine, ifosfamide, and etoposide. Because of the success with chemotherapy in rhabdomyosarcoma, the chemotherapy is started first for large lesions to maximize the response before local treatment. From IRS-I, the complete response rate after 6 weeks of induction chemotherapy alone is about 62%, with another 36% of patients showing a partial response (see Fig. 32-2).[187] In a study from St. Jude Children's Research Hospital, the complete response rate was 7 of 20 (35%) from induction chemotherapy, while the partial response rate was 55%. Only 10% did not respond.[48] The response rate determined by physical examination and radiologic studies is not entirely accurate, since "complete-response" patients may have residual tumor present, whereas a large residual mass may be sterile (see Fig. 32-3).[25,68] There is no evidence that withholding local therapy for 6 to 9 weeks decreases local control or survival.

RESULTS OF TREATMENT. The sites of failure and survival rates in rhabdomyosarcoma of the head and neck are shown in Tables 32-4 and 32-5.[36,151] Orbital lesions have an excellent prognosis, with few local failures and a 5-year survival of greater than 90% for all patients with localized disease at diagnosis. Although the most common approach today is to combine radiation therapy and chemotherapy, radiation therapy alone has been shown to give good results.[164] Unfortunately, with doses of 5000 cGy and above, only 4 of 37 patients treated on IRS-I did not have decreased visual acuity.[74] Local control of all nonparameningeal head and neck rhabdomyosarcomas was 90%, with a 5-year survival of 86% for group I, 84% for group II, and 76% for group III in IRS-II.[36,195]

The parameningeal lesions have the worst rates of local control and the worst prognosis. The treatment of these lesions has undergone a dramatic change over the past 15 years. A report in 1978 from the IRS showed that 20 (35%) of 57 patients with parameningeal rhabdomyosarcomas had recurrence in the central nervous system, even though follow-up was short at that time.[186] Eighteen of the 20 patients had died at the time of the report. Because of the high failure rate, treatment of parameningeal lesions in the IRS-II included 3000 cGy of craniospinal axis irradiation plus intrathecal chemo-

TABLE 32-4. Head and Neck Rhabdomyosarcoma: Sites of Failure by Clinical Group (Intergroup Rhabdomyosarcoma Studies: 2-Year Minimum Follow-Up)

Primary Site	Group	No. of Patients	Site of Failure				
			Primary Site	Regional Nodes	Central Nervous System	Distant Metastasis	Intercurrent Disease
Orbit*	I	1	0	0	0	0	0
	II	10	0	1	0	0	0
	III	20	1	1	0	1	2*
Head and neck (excluding orbit)	I	5	1	0	0	0	0
	II	23	1	1	0	2	0
	III	79	12	0	13	7	8†

* One patient died of treatment toxicity, another of varicella.
† Seven patients died of treatment toxicity, one of unknown causes.
(Adapted from Raney RB, Donaldson MH, Sutow WW, Lindberg RD, Maurer HM, Tefft M. Speciol considerations related to primary site in rhabdomyosarcoma: experience of the Intergroup Rhabdomyosarcoma Study, 1972–1976. NCI Monogr 1981;56:70–72)

TABLE 32-5. Intergroup Rhabdomyosarcoma Studies I and II: 5-Year Survival of Patients With Head and Neck Lesions According to Site and Clinical Group

	IRS Clinical Group[43]							
	I		II		III		IV	
Head and Neck Site	IRS-I	IRS-II	IRS-I	IRS-II	IRS-I	IRS-II	IRS-I	IRS-II
Orbit	100%	100%	95%	91%	88%	90%	50%	0%
Parameningeal	100%	No data	70%	92%	45%	66%	11%	29%
Other	100%	86%	73%	84%	64%	76%	25%	40%

(Modified from Crist WM, Garnsey L, Beltangady MS, Gehan E, Ruymann F, Webber B, Hays DM, Wharam M, Maurer HM. Prognosis in children with rhabdomyosarcoma: a report of the Intergroup Rhabdomyosarcoma Studies I and II. Intergroup Rhabdomyosarcoma Committee. J Clin Oncol 1990;8:447–448)

therapy in the presence of base of skull erosion, cranial nerve involvement, cytology-positive cerebrospinal fluid, or direct intracranial extension. This philosophy improved overall survival from 33% to 57% at 3 years, even with the inclusion of patients with metastases at diagnosis.[154] In a report by Crist and associates, the survival of group II patients with parameningeal lesions was 92% at 5 years; for group III patients, the rate was 66%.[36] The survival of patients with metastases at diagnosis was still poor, with only a 29% 5-year survival in IRS-II.[36] The worst prognostic factor in the parameningeal patients may be extensive base of skull involvement.[117,154]

It has become clear that not all patients with parameningeal lesions require cranial irradiation. In fact, at the present time, only patients with positive cerebrospinal fluid cytology should be treated with cranial irradiation. Even patients with intracranial extension can probably be treated with local fields and a 2- to 3-cm margin, although further follow-up will be necessary to confirm this philosophy.

Fibrosarcoma

Fibroblastic tumors in children present a multitude of unresolved conflicts. There are probably more opinions about their classification than there are affected patients, since they are extraordinarily rare. Still, they represent the most common soft tissue neoplasm in the head and neck in children except for rhabdomyosarcoma, and one to two cases per year will be seen at institutions where a moderate number of patients undergo treatment for pediatric neoplasms.

PATHOLOGY. Most pathologists experienced in the field think that true fibrosarcoma does occur in children and is histologically identical to that occurring in adults. The cell of origin is the fibroblast.

Histologically, elongated, spindle-shaped cells are arranged in a "herringbone pattern" with muscle invasion. A high degree of mitotic activity is present.[142] Heffner noted that the low-grade fibrosarcoma is more cellular than fibromyxoma or aggressive fibromatosis.[71]

The etiology of fibrosarcoma in children is speculative. A few occur in patients with prior irradiation. In addition, patients with bilateral retinoblastoma have a high incidence of sarcomas, particularly osteosarcomas and fibrosarcomas, both with and without prior irradiation.[173] Most fibrosarcomas occur sporadically with no history of prior irradiation or bilateral retinoblastomas. There is a distinct clinical variant of fibrosarcoma in children called congenital or infantile fibrosarcoma by most authors. These lesions are either present at birth or develop within the first year of life.

LOCATION AND ANATOMY. The majority of lesions originate in the extremities, but about 20% of pediatric fibrosarcomas occur in the head and neck region. This is true even for those lesions presenting in the first year of life.[32,135,176]

The neck is the most common primary site of fibrosarcomas above the clavicles; about one third of patients present with this as their primary site. The oral cavity, scalp, auriculoparotid region, and face are the next most common sites, in decreasing frequency. Fibrosarcomas

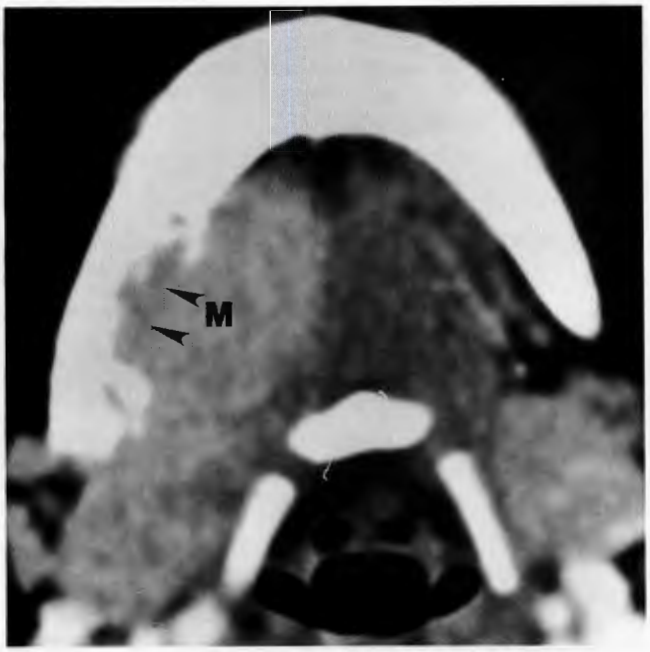

Figure 32-5. A 6-year-old girl had a painless submandibular mass, subsequently proven to be a fibrosarcoma. Axial contrast-enhanced CT shows an ill-defined, moderately enhanced mass (M) in the submandibular space, eroding the mandible (*arrowheads*).

have also been reported in the maxillary sinus, nasopharynx, nasal cavity, and larynx.

PATTERNS OF SPREAD. Locally, fibrosarcomas of the head and neck spread by direct invasion of adjacent tissues. The skin above the lesion is usually not directly involved, but the tumor may occasionally erode underlying bone in the skull, mandible, or neck (Fig. 32-5). Lymph node metastases occur in less than 10% of patients.[183]

The incidence of hematogenous metastasis to lung and bone is reported to be less than 10% for patients under 10 years of age.[32,176] For patients older than 15 years of age, the metastatic rate may approach that of adults, that is, close to 50%.[176]

CLINICAL PICTURE AND WORK-UP. About 36% of pediatric fibrosarcomas are present at birth, while another 13% present in the first year of life. From 1 to 9 years of age, the fibrosarcomas are seen less often, with 2% to 3% of the total lesions presenting at each year of age, but the frequency rises again in the 10- to 16-year age-group. The disease has been reported slightly more often in boys than girls.[176]

Most patients with fibrosarcomas of the head and neck, as well as elsewhere in the body, present with a painless mass (see Figs. 32-5 and 32-6). Some may have tense, shiny, erythematous skin over the lesion. Most patients have a history of a slowly growing mass before diagnosis, but they may present with a rapid growth over a period of weeks and require immediate attention. Other symptoms depend on the location of the disease at the time of diagnosis. Roentgenograms of the lesion may show only a soft tissue mass or may show bone erosion or cortical thickening adjacent to the mass.

The work-up should include an evaluation of the local extent of disease with the appropriate roentgenographic studies, including CT and MRI scans. Neither MRI nor CT can distinguish between malignant fibrous lesions and the more benign variants or mimics such as fibrosing myositis or aggressive fibromatosis (see Fig. 33-8 in Chap. 33). A chest roentgenogram and a bone scan (or skeletal survey for young children) are probably sufficient to rule out metastatic disease, although a CT scan of the lungs may be considered. The yield from these studies will be small, however, particularly in infants.

TREATMENT SELECTION AND TREATMENT RESULTS. Surgery is the most important modality of treatment for pediatric fibrosarcomas, especially those occurring in the first year of life. The extent of surgery

Figure 32-6. (*A*) Fibrosarcoma arising in the right postauricular region in a 10-year-old girl. Two months before this recurrence, the patient had undergone excision of a similar-sized mass. (*B*) Appearance two years after reexcision and postoperative irradiation (6000 cGy was delivered using electrons). Patient had no evidence of local recurrence or distant metastasis.

depends on the age of the child and the location of the tumor. Simple excision has a high recurrence rate; reports in the literature show rates of 40% to 60%.[32,67,173,176] More radical surgery decreases the rate of local recurrence. The rate of distant metastasis is less than 10% in children younger than age 10 and the overall survival rate is good (Fig. 32-7).[32,67,135,173,176] Therefore, in infants, more conservative treatment may be considered to minimize morbidity, especially in the head and neck region. A wide excision with a small cuff of normal tissue is the preferred therapy, with more radical surgery reserved for recurrence. In one series of fibrosarcomas in infants younger than 3 months old, the local recurrence rate was 32%, but the metastatic rate was ultimately only 8%.[12]

Although radiation therapy has often been used postoperatively, the risks involved with treating infants to the appropriate dose should minimize its application.

The prognosis of childhood fibrosarcoma continues to be excellent, even for children up to 10 years of age. At some time above that age, these tumors begin to act more like the adult variety, with much higher rates of distant metastasis, although there is little, if any, difference histologically. Some authors report a survival rate of only 50% above age 10;[173] others report survival to be good up to age 19.[135] Postoperative radiation therapy can increase the rate of local control. Doses in the range of 5000 to 6000 cGy at 170 to 180 cGy per day are appropriate if adequate margins cannot be obtained. There is less experience with preoperative irradiation in children than in adults, but in our experience it is preferable if the surgical margins are not likely to be adequate. A dose of 5000 cGy at 180 to 200 cGy per day is effective, although a twice-a-day regimen has been successfully used at the University of Florida.[13] Prophylactic neck irradiation is not indicated in the presence of a clinically negative neck.

There is little good information on chemotherapy. Drugs such as dactinomycin, methotrexate, cyclophosphamide, vincristine, doxorubicin, ifosfamide, and etoposide have been used for metastatic tumors, but the response rates are poor. Since the main problem initially is a local one, an improvement in survival has not yet been demonstrated by the use of adjuvant chemotherapy, but it may be a reasonable addition to treatment in an older child (older than age 10) with a high-grade or unfavorable lesion. A Pediatric Oncology Group study showed no improvement in survival rates for patients with soft tissue sarcomas other than rhabdomyosarcoma who were treated with adjuvant VAC chemotherapy.[123]

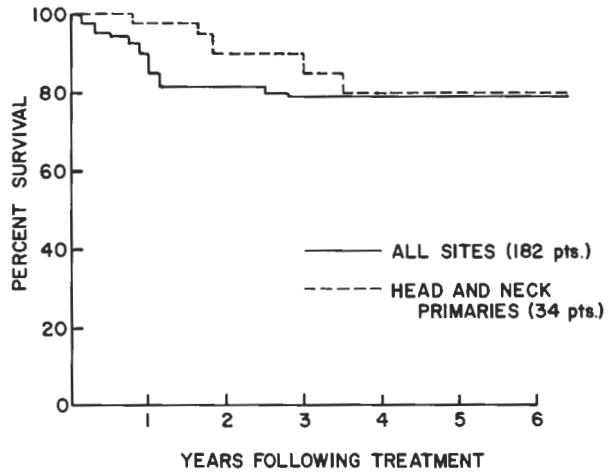

Figure 32-7. Actuarial survival of patients with fibrosarcoma (birth to age 19 years) reported to the End Results Section of the National Cancer Institute before 1971. (Modified by permission from Neifeld JP, Berg JW, Godwin D, Salzberg AM. A retrospective epidemiologic study of pediatric fibrosarcomas. J Pediatr Surg 1978;13:736)

Other Soft Tissue Sarcomas

Except for rhabdomyosarcoma and fibrosarcoma, other soft tissue sarcomas of the head and neck region in the pediatric age group are rare. Although virtually all histologies have been reported to occur, the following three soft tissue sarcomas have some unique features in the pediatric age group. (See Chapter 33 for a discussion of histologies not included here.)

HEMANGIOPERICYTOMA. The pericytes of Zimmermann, which surround the endothelial cells of blood vessels, are thought to be the cells of origin of hemangiopericytomas.

Besides the usual adult variety of hemangiopericytoma, which occurs rarely in older children, an infantile variety has been described.[47] It almost exclusively occurs in children younger than 1 year of age and can be congenital. The tumor starts in the subcutis and is grossly multiloculated. This presents clinically as a painless, rapidly growing mass. Most lesions are solitary, but multiple congenital hemangiopericytomas have been reported in the head and neck.[89,166] Histologically, normal endothelial-lined capillary lumina are surrounded by proliferating cells with round to oval nuclei and moderate nuclear pleomorphism with increased mitotic activity and focal necrosis.[33] Radiologically, calcifications are sometimes seen in the necrotic areas.[89,166]

The treatment of infantile hemangiopericytoma is surgical excision. Local recurrence is uncommon, as is the development of metastatic disease. Death is a rare event, even for patients presenting with multiple lesions.[143]

The children who have the adult variety of hemangiopericytoma are usually in their second decade of life, and there are no data indicating that treatment should be any different from that of adults.

ALVEOLAR SOFT-PART SARCOMA. Alveolar soft-part sarcoma is an unusual tumor of uncertain histogenesis.[31] The tumor presents in children and young adults, most commonly in the third decade. Adult patients tend to have lesions of the extremities, whereas in children the sarcoma is more common in the orbit, tongue, and other sites in the head and neck. Head and neck primary lesions account for 27% of all alveolar soft-part sarcomas in children; 41% of head and neck lesions are in the orbit and 25% are in the tongue.[169] Clinically, orbital lesions produce proptosis, lid swelling, and conjunctival injection. Lesions of the tongue and other sites present as a soft, painless, slow-growing mass and can be easily confused with a hemangioma.

Grossly, the tumor is well vascularized and circumscribed, but unencapsulated. Histologically, there are uniform, compact cell clusters with numerous vascular channels surrounded by connective tissue septa, or an alveolar form with a central space lacking organized material ("soft part"). Mitotic figures are rare. Batsakis considered the light-optic characteristics to be almost

pathognomonic.[6] Periodic acid–Schiff-positive crystalline rods within the cytoplasm are present in at least 80% of these tumors.[162]

The natural history of these tumors is long. They are slow to grow, often recur locally, and may metastasize to regional nodes and distant sites.[174]

The treatment of choice is surgery, with adjuvant irradiation necessary if the margins are not adequate. Short-term survival is fair, with 59% of patients alive at 5 years and 47% alive at 10 years.[108] Recurrences beyond 10 years are not uncommon, and the long-range survival may be much lower.

SYNOVIAL CELL SARCOMA. Overall, synovial cell sarcoma is the most common soft tissue sarcoma (excluding rhabdomyosarcoma) in children, but most lesions occur in the extremities. Fewer than 50 cases have been reported in the head and neck.[132] Synovial sarcoma may occasionally occur in the neck in the pediatric age-group. This is a disease of young men, with an average age of 19 years according to one series.[160]

The treatment is primarily surgical, but in the series reported by Roth and associates the tumor was controlled locally in only 7 of 17 patients who initially had surgery alone.[160] Many of them probably had inadequate surgery by today's standards. Postoperative irradiation is necessary for most lesions, since radical surgical margins are difficult to obtain in the head and neck. Doses in the range of 5000 to 6000 cGy at 180 to 200 cGy per day are recommended.

About half of the patients with primary lesions in the neck survive 5 years.[64,160] Most deaths are caused by pulmonary metastases, but many patients who die of distant metastases develop local recurrence first.

Bone Sarcomas

Bone sarcomas represent about 4.5% of all malignant childhood tumors. Osteosarcoma is the most common, representing 63% of pediatric bone tumors. Ewing's sarcoma accounts for another 27%, while chondrosarcoma and other rare bone tumors make up the remaining 10%.[201] These figures do not include primary lymphomas of bone.

Osteosarcoma

Osteosarcomas account for 2.6% of all pediatric malignant tumors and 63% of malignant bone tumors in childhood.[201] Seven percent to 16% of osteosarcomas occur in the head and neck, although most of these are in adults.[39,79]

Prior radiation therapy, Paget's disease, fibrous dysplasia, and bilateral retinoblastoma (even without radiation therapy) predispose to the development of osteosarcoma in the head and neck.

LOCATION. The distribution for 329 head and neck lesions is shown in Figure 32-8. The body of the mandible is most commonly involved, then, in descending frequency, the symphysis, angle, and ascending ramus. In the maxilla, the alveolar ridge and antrum are the most common sites. Involvement of the base of the skull or cervical spine is a rare occurrence. Soft tissue lesions of the parotid region, larynx, thyroid, and tongue have also been reported.

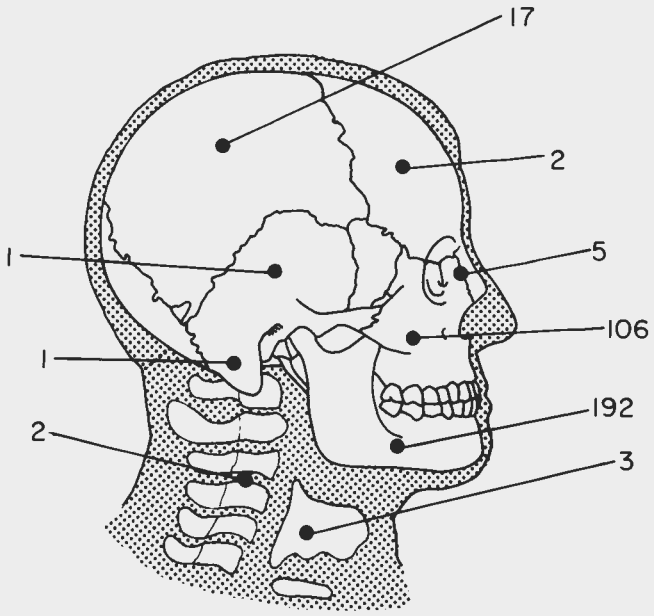

Figure 32-8. Location of 329 cases of osteosarcoma of the head and neck. Data were collected from literature from 1940 to 1982 in which location of the lesion was well specified.

PATTERNS OF SPREAD. By the time an osteosarcoma is diagnosed, it has generally breached the cortex and an extraosseous mass is present, which invades the surrounding soft tissues. The most common site of metastatic disease is the lung, although bone metastases are not uncommon.

CLINICAL PICTURE. Osteosarcoma of the head and neck appears to present at a later age than osteosarcoma of the extremities. Whereas 66% of osteosarcomas of the long bones occur in patients younger than 20 years of age, head and neck lesions have a roughly even distribution by decade from 10 years of age to 50. The male-to-female ratio is about 1 : 1, and there does not appear to be any major racial predisposition.

Most osteosarcomas present as pain in the involved bone. This is usually mild and transitory at first, but gradually develops into a more persistent, and at times severe, pain. When the tumor breaks through the cortex of the bone into the soft tissues, a large mass may be noticed by the patient. The mass may be rock hard, but a soft or rubbery mass does not exclude osteosarcoma in the differential diagnosis.

Roentgenographic findings vary greatly. Tumors may be either primarily sclerotic or primarily lytic, but they usually have a combination of these features. The lytic lesions are usually more painful than the sclerotic ones. The destructive process usually involves the cortex with a gradual transition from zones of marked lysis to zones of uninvolved bone, making the border indistinct. The periosteum is often elevated by penetrating tumor, and a soft tissue mass may be visible on roentgenograms but is best evaluated by a combination of MRI and CT. There are often amorphous calcium deposits in the soft tissue mass as the growing tumor attempts to lay down an abnormal bone matrix.

Symmetric widening of the periodontal ligament involving one or more teeth may be a clue to a developing osteosarcoma or chondrosarcoma of the mandible.[56]

Root resorption of a permanent erupted tooth is unusual for an osteogenic sarcoma, being more common as a result of inflammation or a benign tumor.[40]

STAGING. A complete evaluation should be undertaken *before the biopsy is done* for suspected osteosarcoma. In addition to plain roentgenograms of the involved site, the local disease can also be evaluated with CT, MRI, and occasionally angiography to determine the status of the neurovascular bundle adjacent to the tumor.

The overwhelming majority of metastatic disease appears first in the lungs. A chest roentgenogram plus a CT scan of the lung is an effective way of detecting small foci of disease in the lung.

A bone scan is useful in determining the extent of local disease as well as in detecting metastatic bone lesions.

The level of serum alkaline phosphatase is usually elevated, and patients whose levels remain high after surgical resection should be strongly suspected of harboring metastatic disease. This test is also used in the follow-up, since a rise in alkaline phosphatase after treatment has been correlated with the development of metastatic disease or a local recurrence. In children, and particularly in adolescents, the serum alkaline phosphatase level is normally high, and caution must be used in interpreting a slightly elevated alkaline phosphatase level in that age-group.

SELECTION OF TREATMENT MODALITIES. The risk of distant metastases is less for head and neck primary lesions than in other sites (Table 32-6). The emphasis of treatment is therefore local control. Surgical excision is recommended if the lesion presents in a resectable site such as the mandible, maxilla, or skull, but surgery alone is often inadequate and may be combined with preoperative or postoperative radiation therapy.

Chemotherapy has proven to increase survival in osteosarcomas of the extremities, but its usefulness in head and neck lesions is unknown.[111] For more favorable lesions, such as those in the mandible or alveolar ridge of the maxilla, adjuvant chemotherapy is probably of minimal value; few of these patients develop distant metastases until after one or more local failures. For lesions of the maxillary antrum, skull, cervical spine, and other rare sites in the head and neck, the prognosis is so poor that it is worthwhile to consider aggressive therapy with surgery (if possible), irradiation, and chemotherapy.

SURGERY. Of the lesions arising in the head and neck, mandibular osteosarcomas are most amenable to surgical resection, and resection of the involved portion of the mandible with surrounding soft tissue is recommended by some authors, while others recommend hemimandibulectomy, since local failure remains the biggest problem in controlling disease in this site (see Table 32-6). For a few small lesions of the mandible, reconstruction can be done after the initial resection, but if soft tissue extension is present, reconstruction may not be possible. Maxillary lesions starting on the alveolar ridge usually can be resected by a limited maxillectomy, but lesions arising elsewhere in the maxilla (ie, "antral primaries") may require a maxillectomy with or without an orbital exenteration. More extensive lesions may require a craniofacial procedure (see Chap. 22). Surgery is also the treatment of choice for laryngeal or parotid lesions. For lesions arising in the skull, surgery becomes more difficult, although still possible in most cases. For lesions arising in the base of the skull or cervical spine, surgery is usually not possible, and these masses must be treated with radiation therapy.

RADIATION THERAPY. Radiation therapy is usually recommended in combination with surgical resection because of the high rate of local failure after resection alone (see Table 32-6). The radiation therapy is usually given postoperatively in full therapeutic doses (7000 to 7500 cGy at 180 to 200 cGy per day). Preoperative radiation therapy (5000 to 6000 cGy at 180 to 200 cGy per day) is selected for lesions that are not technically resectable in the hope that sufficient regression may be followed by total resection. In these cases, preoperative chemotherapy may also be considered, although information on such an approach is lacking.

For lesions that are inoperable, an occasional cure with radiation therapy alone has been reported.[41,54,104] The dose required for control is not clear. Usually, doses in the range of 7000 to 8000 cGy over 7 to 9 weeks are required, but the constraints of central nervous system tolerance limit the dose that can be delivered to lesions of the cervical spine and base of the skull. Lower doses may sometimes be effective, at least for extending survival, particularly in conjunction with chemotherapy.[84] Special treatment programs with particles (protons) may be used to minimize the dose to the brain stem or spinal cord. Combinations of surgery, radiation therapy, and chemotherapy have been used in spinal lesions, resulting in an occasional cure.[178]

CHEMOTHERAPY. The most effective drugs against osteosarcoma are methotrexate, doxorubicin, cisplatin,

TABLE 32-6. Osteosarcoma of the Head and Neck: Site of Failure (Data Collected From the Literature, 1940 to Date; 5-Year Minimum Follow-Up)

Primary Site	No. of Patients	Site of Foilure		
		Local Recurrence	Local Recurrence + Distant Metastasis	Distant Metastasis
Mandible	49	21 (43%)	6 (12%)	6 (12%)
Maxilla				
Antrum	11	6 (55%)	4 (36%)	0 (0%)
Alveolar ridge	19	7 (37%)	5 (26%)	2 (11%)
Skull* and miscellaneous sites	14	4 (29%)	4 (29%)	5 (36%)

* Two-year minimum follow-up.

and ifosfamide. Most adjuvant regimens include two or more of these drugs.[83]

RESULTS OF TREATMENT. Preoperative external-beam irradiation in doses of 5000 to 6000 cGy is probably of value.[177] The local control rate (5-year minimum follow-up) collected from the literature is better for those who received preoperative radiation therapy (8 of 13, 62%) than for surgery alone (17 of 44, 39%). Ninety percent of local failures occur within the first 2 years.

Actuarial survival by primary site for skull, maxillary, and mandibular lesions is shown in Figure 32-9.

Ewing's Sarcoma

Ewing's sarcoma is a distinctive, small round cell tumor that occurs primarily in the first three decades of life. It is uncommon in the head and neck region. Of 117 patients treated at the University of Florida from 1969 through 1989, only 6 had primary lesions above the clavicles. Dahlin, in reviewing 299 Ewing's sarcomas seen at the Mayo Clinic before 1975, reported only 8 occurring above the clavicles.[39] Of 805 patients entered on four protocols of the Intergroup Ewing's Sarcoma Study, 29 patients with primary lesions of the head and neck were identified.[169]

Blacks in both the United States and Africa are rarely afflicted.[57,196]

PATHOLOGY. Ewing's sarcoma is a primitive malignant tumor of bone, characterized by anaplastic small cells with round nuclei without distinct cytoplasmic borders or prominent nucleoli. The cells are usually glycogen positive.

Although there is no definitive proof of the origin of Ewing's sarcoma, evidence exists that points to a neuroectodermal origin.[28,198] It may well be part of a spectrum of small round cell tumors that includes primitive neuroectodermal tumor or peripheral neuroepithelioma of bone and Askin's tumor (small cell tumor of the thoracopulmonary region). These latter two may represent intermediate stages of differentiation of more typical Ewing's sarcomas.

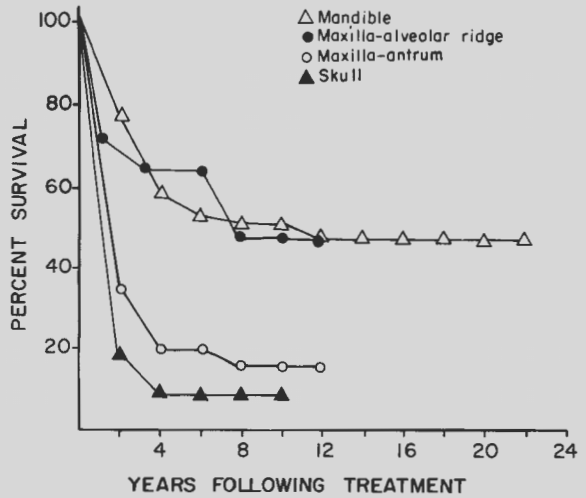

Figure 32-9. Actuarial survival by primary site of 206 patients with osteosarcoma of the head and neck. Data were collected from literature from 1940 to 1982 in which length of survival and primary site were clearly stated.

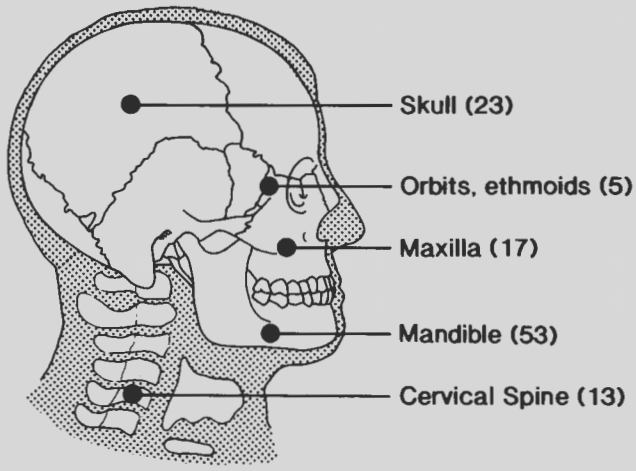

Figure 32-10. Location of 111 cases of Ewing's sarcoma of the head and neck. Data were collected from literature from 1950 to 1989 in which location of the lesion was well specified. Six patients from the University of Florida are included.

LOCATION. The distribution of 111 cases of Ewing's sarcoma of the head and neck reported in the literature from 1950 to date is shown in Figure 32-10. In both the mandible and maxilla, the posterior parts of the jaw are the preferred sites of involvement.[199]

PATTERNS OF SPREAD. The medullary cavity appears to be the site of origin of most Ewing's sarcomas. Even in early stages of disease, however, the cortex may be eroded and a large, friable, hemorrhagic, soft tissue mass can develop. In later stages of disease, almost all tumors will exhibit a soft tissue mass that encircles and envelops the involved portion of the bone. Mandibular primary lesions tend to spread laterally into the soft tissues of the masseter muscles instead of medially into the oral cavity. A primary lesion of the mandible that did invade the floor of the mouth is shown in Figure 32-11. Lesions of the cranium are usually slow to invade the dura and brain, preferring instead to grow outward. Cervical spine lesions tend to compress the cord early in the course of the disease. Cervical lymph node involvement is uncommon. The most common sites of distant metastasis are the lung, skeleton, and bone marrow.

CLINICAL PICTURE. Ewing's sarcoma of the head and neck most commonly presents between the ages of 6 and 20 years, with close to a 2 : 1 male to female predominance.

Most patients present with pain or an asymptomatic mass. Often, there is a history of a rapidly increasing mass followed by a stable period lasting for a few weeks or many months. There is often local temperature elevation over the mass. In mandibular lesions, dental problems may be the first sign of the tumor, and the patient may present to the dentist. Involvement of the inferior alveolar nerve may cause paresthesias of the lips and chin. Patients with maxillary primary lesions often present with nasal obstruction, dental problems, swelling of the zygomatic region, exophthalmos, and tearing.[52]

Systemic symptoms are occasionally present, with a slight to moderate fever, anemia, leukocytosis, and an increased sedimentation rate. These symptoms may herald spread to bone marrow or other distant sites, but

Figure 32-11. Ewing's sarcoma arising in the mandibular symphysis in a 12-year-old girl. (*A*) Lateral roentgenogram. (*B*) Soft tissue extension into the floor of mouth (*arrows*). (*C*) Patient was treated with radiation therapy and received 5200 cGy to the entire mandible using lateral opposed cobalt-60 fields; the primary site received 5600 cGy. She also received adjuvant chemotherapy in the form of cyclophosphamide and vincristine. Three years after therapy, the profile of her face was normal. (*D*) Ten years after therapy, hypoplasia of the mandible secondary to irradiation was visible. (*E*) Ten years after radiation therapy, the floor of mouth appears normal. There was crowding of the mandibular incisors secondary to hypoplasia of the mandible.

they also occur in what appears to be localized disease. They are a poor prognostic sign.

The usual roentgenographic appearance of Ewing's sarcoma in the head and neck is that of a lytic or mottled pattern of bone destruction with poorly defined margins. A few lesions are predominantly sclerotic.[199]

STAGING. The evaluation involves roentgenograms of the primary site, including the whole bone involved, with careful analysis of the extent of disease by CT scan and MRI. A Panorex view of the mandible is useful in evaluating lesions originating there.

A complete blood cell count and sedimentation rate determination are necessary to evaluate systemic disease. A chest roentgenogram and a CT scan of the lung are important to rule out metastatic lung disease. A bone scan as well as bone marrow aspiration and biopsy are necessary to evaluate possible spread to other bones and the bone marrow.

SELECTION OF TREATMENT MODALITIES. Radiation therapy is the principal modality used for the local treatment of Ewing's sarcoma of the head and neck. Small mandibular lesions may occasionally be selected for surgery, but most other lesions are best treated with irradiation. In an ongoing (though nonrandomized) study of the German Cooperative Ewing's Sarcoma Group comparing radiotherapy alone, surgery alone, and surgery plus radiotherapy, there is no difference in relapse-free survival to date.[44]

All patients should receive systemic chemotherapy. In the past, chemotherapy and radiation therapy have been started concomitantly, but at present the choice at many institutions is to give two to five cycles of chemotherapy before local treatment. Not only will most soft tissue masses disappear, but also areas of bone destruction will usually begin to heal. Chemotherapy should be continued during radiation therapy and for 6 to 12 months afterward, depending on the regimen employed.

RADIATION THERAPY. There is no definite dose–response curve for Ewing's sarcoma (Table 32-7).[156] Since the early 1970s, the beginning of the chemotherapy era, most trials have used the following regimen: 3500 to 4000 cGy to the entire involved bone, followed by a 1000- to 1500-cGy boost to the lesion itself, for a total dose of 5000 to 5500 cGy at 180 to 200 cGy per fraction. It is not necessary to treat the contralateral hemimandible in a patient with a small unilateral lesion.

At the University of Florida, a hyperfractionation regimen has been used since 1982. Using 120 cGy twice a day, a dose of 3600 cGy is given to the primary lesion plus a generous margin, followed by a boost of 1440 to 2400 cGy, again at 120 cGy twice a day, for a total dose of 5040 to 6000 cGy.[119] The 2-year local control rate with this approach has been over 90% when aggressive systemic treatment was given (including total-body irradiation for high-risk patients), and the functional results have been excellent.

TABLE 32-7. Correlation of Local Control With Irradiation Dosage (Intergroup Ewing's Sarcoma Study—All Sites)

Tumor Dose (cGy)	No. Controlled/No. at Risk (%)
3000–3999	6/6 (100)
4000–4999	37/43 (86)
5000–5999	80/91 (88)
≥6000	50/53 (94)

(Adapted from Razek A, Perez CA, Tefft M, Nesbit M, Vietti T, Burgert EO Jr, Kissane J, Pritchard DJ, Gehan EA. Intergroup Ewing's Sarcoma Study: local control related to radiation dose, volume, and site of primary lesion in Ewing's sarcoma. Cancer 1980;46:519)

CHEMOTHERAPY. The drugs most commonly used in the treatment of Ewing's sarcoma are vincristine, cyclophosphamide, ifosfamide, dactinomycin, doxorubicin, and etoposide, although other drugs are known to be active. All have good activity against the tumor as single agents. Most regimens for the treatment of Ewing's sarcoma use a combination of these drugs.[3,10,30,66,88,120,131,137,141,145–147,203]

Bone marrow depression is one of the major side effects of all regimens. With lesions near the oral cavity, severe confluent mucositis secondary to the combination of radiation therapy and doxorubicin or dactinomycin may render the child virtually incapable of eating and require admission to the hospital for nutritional supplementation.

RESULTS OF TREATMENT. The survival of patients with Ewing's sarcoma has improved dramatically with the advent of systemic chemotherapy. Whereas the prechemotherapy survival rate was about 5% at 5 years,[148] even for patients with localized disease, adjuvant chemotherapy has increased the rate significantly,[30,137,147,158] although survival at 5 years remains less than 50% in most series.[94,118,122]

Although there are few data available for intensive analysis, head and neck lesions are generally regarded as a favorable site. The survival of patients with head and neck primary lesions is shown in Figure 32-12 for patients treated on the Intergroup Ewing's Sarcoma Study (IESS) protocols. With adjuvant chemotherapy, the prognosis was good for all head and neck sites, with the possible exception of the cervical spine.[168]

A large extraosseous mass has been shown to produce a much poorer prognosis, regardless of the primary site. Size may be the most important prognostic factor, however, with large (greater than 8 cm or greater than 100 cm^3) tumors resulting in a 5-year survival rate of 20% to 30%. Head and neck lesions, for the most part, are small enough to fall within the favorable group.[88,121,129]

A few patients who present with metastatic disease can be cured with intensive chemotherapy and radiation therapy.[66,120,131] Most successes occur in patients who have either a single bony or lung metastasis, and these patients warrant aggressive treatment with radiation therapy to all sites of gross disease as well as concomitant chemotherapy. Although those with multiple bony metastases at diagnosis continue to do dismally, aggressive treatment ending with ablative chemotherapy and radiation therapy and an autologous (or allogeneic) bone marrow transplant may improve survival rates in those patients with large primary lesions.[120,131]

Chondrosarcoma

In the Mayo Clinic series, of 470 patients with chondrosarcoma, only 17 presented in the second decade and only 3 were younger than 10 years of age.[39] In general, the treatment principles are the same for the pediatric age group as they are for adults, and this is covered in more detail in Chapter 33.

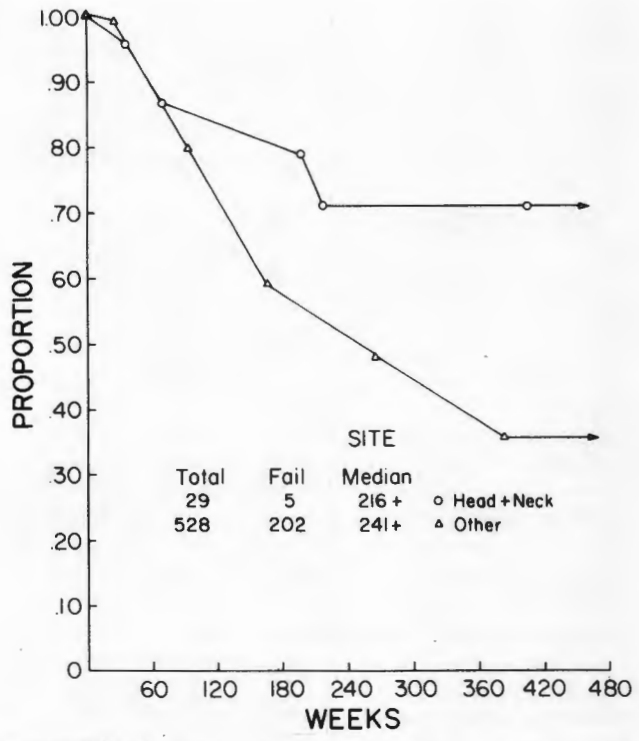

Figure 32-12. Relapse-free survival of patients with Ewing's sarcoma of the head and neck treated on the First and Second Intergroup Ewing's Sarcoma Studies. (Siegal GP, Oliver WR, Reinus WR, Gilula LA, Foulkes MA, Kissane JM, Askin FB. Primary Ewing's sarcoma involving the bones of the head and neck. Cancer 1987;60:2839)

Neuroectodermal Tumors

Neuroblastoma

Neuroblastoma is the most common extracranial malignant solid tumor in infancy and childhood, but only 5% of all primary lesions occur in the head and neck. Twenty-five percent to 30% of neuroblastomas present in patients younger than 1 year of age, with another 15% to 20% at 1 to 2 years of age. Over half are older than 2 years of age at diagnosis, but only a rare patient is older than age 5.[14]

Neuroblastoma arises from primordial neural crest cells.[165] It is the most malignant variant of a spectrum of tumors that also includes the ganglioneuroblastoma and the benign ganglioneuroma.

The most common site of primary neuroblastoma in the head and neck is in the cervical sympathetic chain. The only other common site in the head is the olfactory bulb, but this tumor, called the esthesioneuroblastoma, primarily occurs in adults (see Chap. 22).

In addition, neuroblastoma may metastasize to the head and neck area. Bilateral proptosis or supraorbital ecchymoses from bilateral orbital involvement (Fig. 32-13) are not uncommon, and the cranium is the most common site of bony metastasis. Cervical neuroblastoma spreads locally by invading the surrounding tissues. It may also pass through the neural foramina into the spinal canal, thus causing neurologic sequelae.

Neuroblastoma also has a high propensity to spread to regional nodes. The most common sites of distant metastases are the bone marrow, bony cortex, liver, and skin.

Neuroblastoma commonly presents as a painless mass. In the neck, this can be a lymph node, but more commonly it is a deeper mass that feels fixed to the underlying vertebral structure of the neck. Patients with "dumbbell" tumors may present with neurologic symptoms, although complete obstruction has occasionally been demonstrated by myelography in patients with no neurologic symptoms. Horner's syndrome is common at diagnosis.

The most common staging system used is the Evans system, although the Pediatric Oncology Group staging system is also widely used.[27,49]

The two most important determinants in survival are the age of the patient and the stage of disease at diagnosis (Table 32-8).[14] It seems clear that for young patients with resectable disease, complete excision offers the best chance for cure, with 90% or more younger than 1 year of age surviving. Chemotherapy is used in conjunction with surgery in older patients (older than age 1 year).

Unresectable primary lesions, even when still localized at diagnosis, have a much poorer prognosis and generally occur in older patients. Radiation therapy in doses of 2000 to 3000 cGy at 150 to 180 cGy a day is useful in these lesions.[27,81]

For patients with metastatic disease at diagnosis, survival rates are dismal at any age, although an occasional patient younger than 1 year of age may survive.[14,72] Autologous bone marrow transplantation may cure some patients with advanced disease at diagnosis.[59]

Malignant Melanotic Neuroectodermal Tumor of Infancy

Over 160 cases of this unusual tumor of early infancy have been reported since its original description by Krompecher in 1918.[98] The tumor has masqueraded un-

Figure 32-13. An 18-month-old girl had typical supraorbital ecchymoses secondary to bilateral orbital metastases from neuroblastoma.

TABLE 32-8. Percentage Survival in Neuroblastoma According to Age and Evans Stage

Age (Years)	Stage I (Localized, Confined to Organ of Origin)	II (Localized, Spread Beyond Organ of Origin)	III (Localized, Spread Across Midline)	IV (Distant Metastasis)	IVS (Distant Metastasis Confined to Bone Marrow, Skin, Liver)
<1	97	89	82	26	91
1–2	77	49	36	4	54
>2	67	37	26	3	42

(Modified from Breslow N, McCann B. Statistical estimation of prognosis for children with neuroblastoma. Cancer Res 1971;31:2099)

der a variety of names, including pigmented ameloblastoma, pigmented congenital epulis, melanotic ameloblastic odontoma, melanotic progonoma, retinal anlage tumor, congenital melanocarcinoma, and retinoblastic teratoma. These terms reflect the various proposed theories of histogenesis. Now, however, morphologic analysis by electron microscopy[38] and reports of vanillylmandelic acid secretion support a neural crest origin. The tumor is grossly blue-black or black, with two major populations of cells identified by light microscopy. One group is small, with dense nuclei and sparse cytoplasm; the other cell type consists of larger cells with pale nuclei with abundant cytoplasm.[5,37]

The maxilla is the site of origin in 80% of cases, with the mandible being the second most common site. Rare cases of infraclavicular sites have been reported.[38] Ninety-five percent of cases present before 1 year of life. The classic clinical presentation is that of a firm, painless, rapidly growing mass in the premaxilla of an infant. The tumor elevates the upper lip and can interfere with nursing. The overlying mucosa is generally normal. Radiographically, a lucent area displacing the deciduous teeth is seen. Treatment is surgical with a local recurrence rate of 10% to 15%. A metastatic rate of 3% has been reported.[5]

BENIGN LESIONS

Langerhans' Cell Histocytosis

Langerhans' cell histiocytosis (previously called histiocytosis X) appears to arise from Langerhans cells. The histiocytoses are not technically thought to be cancer and, indeed, are often self-limited with little or no treatment. In some children, however, the disease is lethal, even with aggressive multimodal therapy.

The mortality of the disease is primarily age dependent (Fig. 32-14).[57] There is no obvious sex predilection, but a familial incidence has been reported.[130] Langerhans' cell histiocytosis is now believed to be an autoimmune disorder, and there is an associated immune deficiency, at least in some patients.[136]

Syndromes

The differentiation of several forms of the disease is primarily a clinical and not a histologic one.

Eosinophilic granuloma is the most benign of the entities and represents a solitary presentation of the disease. It occurs most often in the skull or long bones, although it can occur in a soft tissue site, often in the central nervous system.[92]

Disseminated forms of the disease have been classified in the past as either Hand–Schüller–Christian syndrome or Letterer–Siwe syndrome. Hand–Schüller–Christian disease encompasses the triad of exophthalmos, membranous bone defects, and diabetes insipidus, whereas the Letterer–Siwe type has widespread organ involvement. Because of the overlap of the various syndromes, as well as the fact that one syndrome may evolve into another, other staging and grouping systems have been suggested. No matter which staging system is used, it is clear that there is a good-risk group consisting of solitary bone lesions and a poorer-risk group with disseminated disease.

Location

In review of the world literature, the skull is found to be the most common site for the presentation of localized histiocytosis (eosinophilic granuloma) of bone, with 27%

Figure 32-14. Mortality per year from disseminated histiocytosis in white children, by age at diagnosis (United States, 1960–1964). (Glass AG, Miller RW. US mortality from Letterer-Siwe disease. Pediatrics 1968;42:365. Copyright © 1968, American Academy of Pediatrics)

of patients having lesions there.[18] The mandible alone is the primary site in 6% of patients. Soft tissue primary lesions in the oral cavity, nasopharynx, and elsewhere in the head and neck have been reported.

The disseminated forms of the disease involve the same sites in about the same relative frequency (Fig. 32-15).

Clinical Picture

The most common presentation for localized histiocytosis (eosinophilic granuloma) is pain or swelling in the local area. Destruction of the temporal or mastoid bones may simulate chronic otitis media. Infiltration of the maxilla and mandible may cause dental symptoms such as loose teeth or pain. Frontal or orbital masses may cause proptosis and visual dysfunction. Sphenoid bone and sella turcica involvement may cause pituitary dysfunction, particularly diabetes insipidus. Diabetes insipidus may occur secondary to focal disease in the hypothalamus or pituitary without attendant bony involvement, however. Localized histiocytosis usually occurs in older children and young adults (Fig. 32-16).

The chronic disseminated form of the disease is primarily confined to bone, with multiple bones usually involved. In addition to bony involvement, however, severe seborrhea is also common, and a typical scaly, maculopapular rash, which spreads from the ear to involve both cheeks and neck, is not infrequent.

The acute disseminated form of the disease is frequently misdiagnosed because the initial signs and symptoms are varied and mimic other diseases. It usually occurs in infants and frequently produces fever of unknown origin, poor appetite, weight loss, failure to thrive, irritability, and lethargy. A maculopapular rash with a hemorrhagic base may be prominent, along with

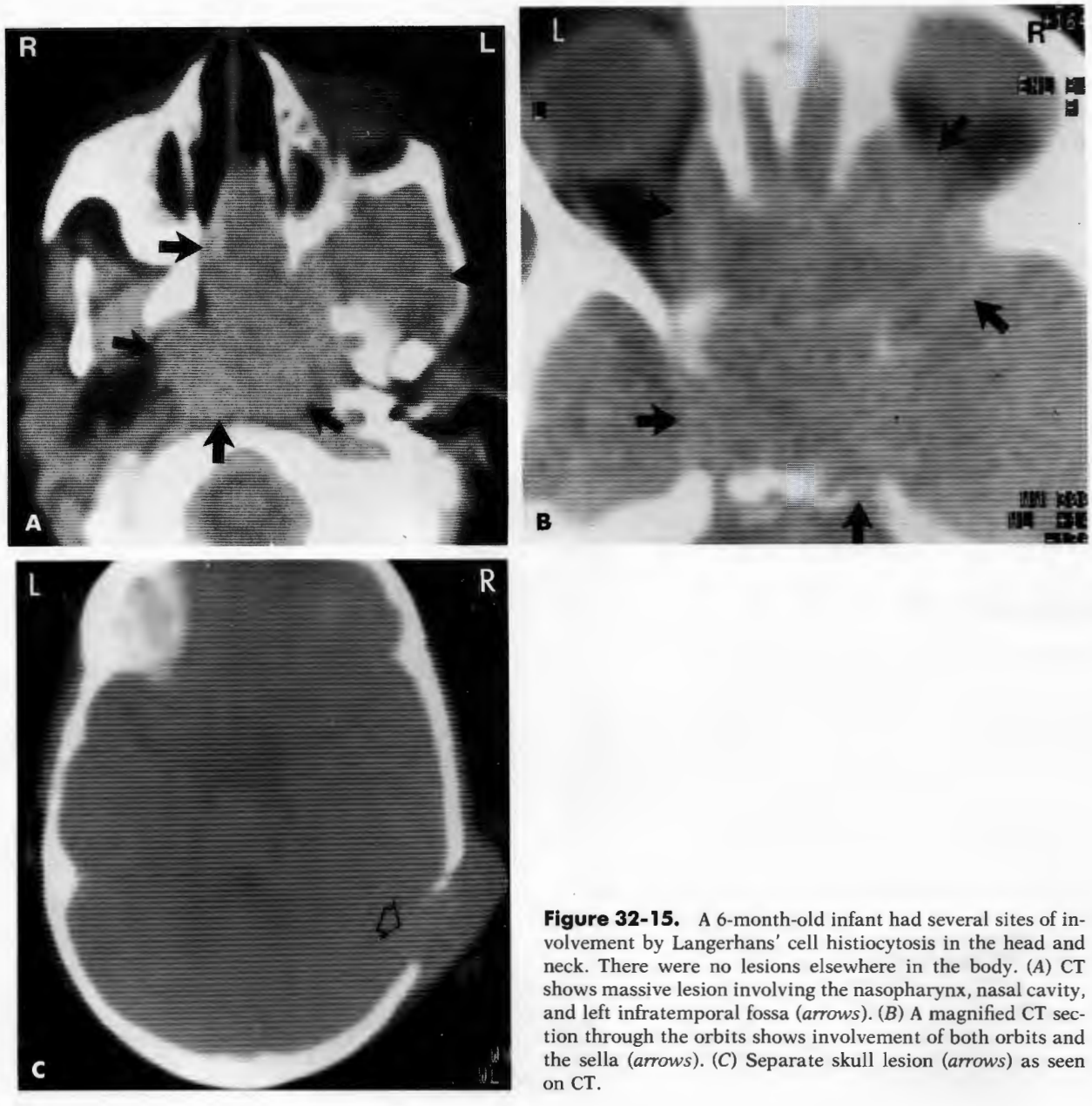

Figure 32-15. A 6-month-old infant had several sites of involvement by Langerhans' cell histiocytosis in the head and neck. There were no lesions elsewhere in the body. (*A*) CT shows massive lesion involving the nasopharynx, nasal cavity, and left infratemporal fossa (*arrows*). (*B*) A magnified CT section through the orbits shows involvement of both orbits and the sella (*arrows*). (*C*) Separate skull lesion (*arrows*) as seen on CT.

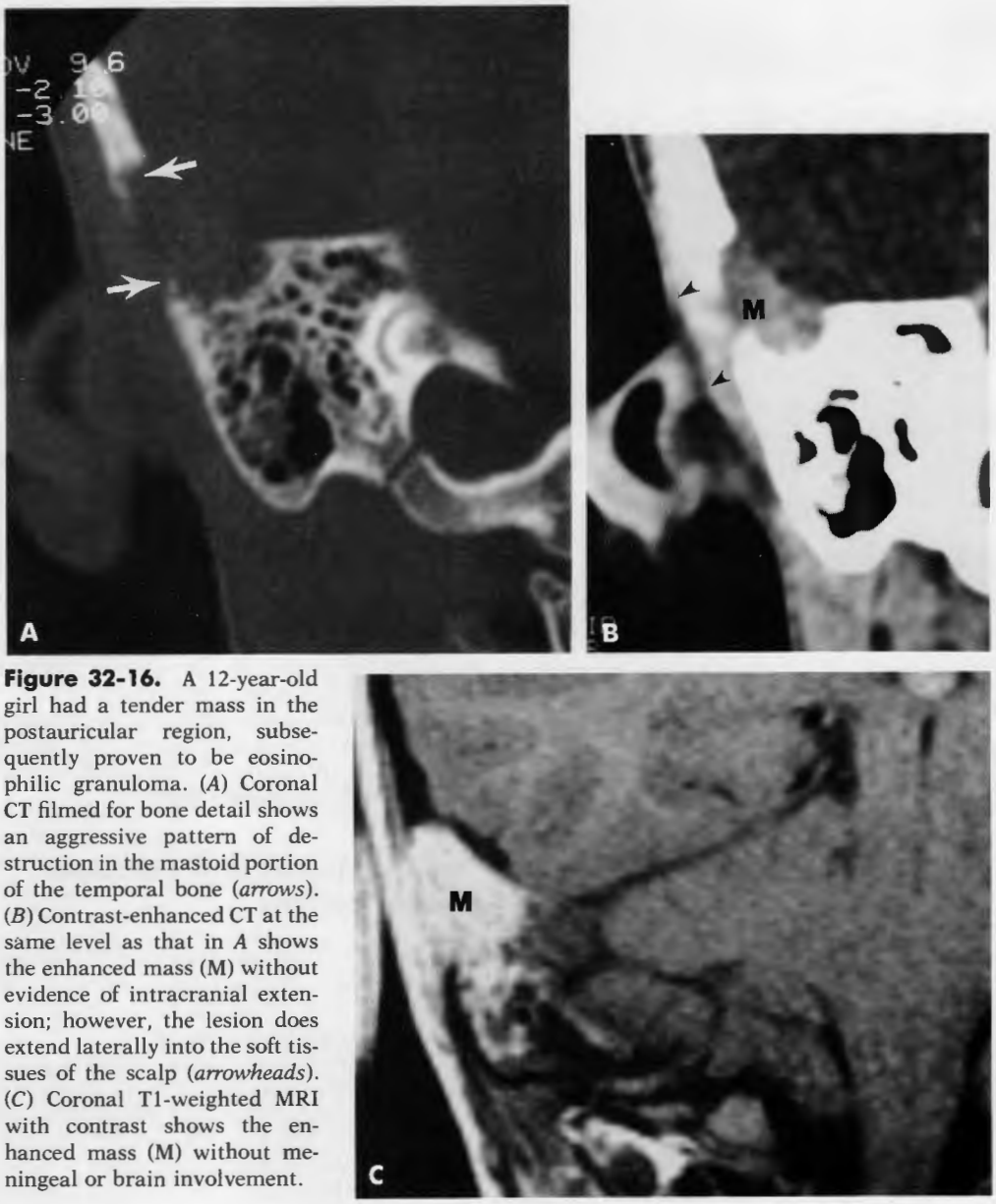

Figure 32-16. A 12-year-old girl had a tender mass in the postauricular region, subsequently proven to be eosinophilic granuloma. (*A*) Coronal CT filmed for bone detail shows an aggressive pattern of destruction in the mastoid portion of the temporal bone (*arrows*). (*B*) Contrast-enhanced CT at the same level as that in *A* shows the enhanced mass (M) without evidence of intracranial extension; however, the lesion does extend laterally into the soft tissues of the scalp (*arrowheads*). (*C*) Coronal T1-weighted MRI with contrast shows the enhanced mass (M) without meningeal or brain involvement.

adenopathy and organ involvement. The liver and spleen can be massively enlarged, and the lung is also commonly involved. The acute disseminated form often pursues a malignant, rapidly fatal course, particularly in children younger than 2 years of age, the age at which it occurs most commonly.

Staging

There have been several suggested staging systems for histiocytosis, but none has been commonly accepted.[61,95,100] The one proposed by Komp and coworkers is simple and of prognostic value (Fig. 32-17).[95]

Many of the lesions of histiocytosis, particularly those in the head and neck, can be found with a careful physical examination. The skull should be palpated, searching for bony involvement, and careful attention should be given the middle ear, eyes, orbits, and oral cavity. Laboratory studies include a complete blood cell count, platelet count, sedimentation rate, liver function studies, renal function studies, and a urine specific gravity. A water deprivation test should be performed if there is suspicion of diabetes insipidus.

Roentgenographically, a chest roentgenogram and skeletal survey are essential. Histiocytosis remains one disease where conventional roentgenograms can be more sensitive than a bone scan, which may be normal even with multiple bony lesions. Roentgenographically, most bony lesions are lytic, with no sclerotic border until they begin to heal. Other studies to consider are a bone marrow aspiration and biopsy, Panorex films of the mandible and maxilla, and immunologic studies.

Treatment Selection and Treatment Results

The usual treatment of a single bone lesion is biopsy with curettage. As many as 70% of the lesions will heal after such treatment.[8,109,125] For progressive lesions and

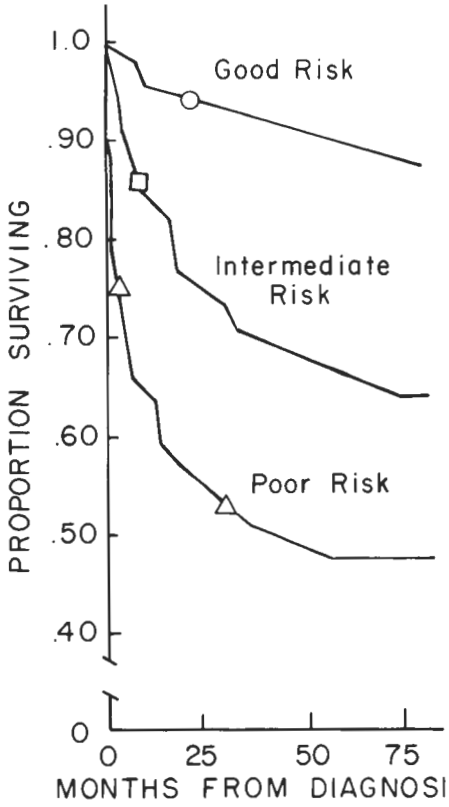

Figure 32-17. Survival of patients with disseminated histiocytosis using the following staging system: good risk: older than 2 years of age with no organ dysfunction; intermediate risk: younger than 2 years of age with no organ dysfunction; poor risk: organ dysfunction at any age. (Komp DM, Herson J, Starling KA, Vietti TJ, Hvizdala E. A staging system for histiocytosis X: a Southwest Oncology Group study. Cancer 1981;47:799)

those that cause symptoms at diagnosis, such as severe otitis media or exophthalmos, radiation therapy is recommended, and if radiation therapy can be instituted soon after the onset of diabetes insipidus, it may be possible to reduce this complication of the disease.[61] The dose of radiation is not clear. Treatment has been reported to be successful with as little as 300 cGy, but occasional failures have been noted with doses of 3500 cGy.[159,171] It certainly appears that a dose of 600 to 900 cGy is adequate for 85% to 90% of the lesions.[171] It can be given at a rate of 150 to 200 cGy per day with minimal risk of acute or late side effects and the treatment can usually be repeated in the event of persistent disease. The prognosis of isolated eosinophilic granuloma is very good. It is rare to see a patient die of this disease. In a review of 686 cases of eosinophilic granuloma by Slater and Swarm, only nine patients died.[170] Even patients who relapse usually survive, whether the relapse is local or distant. It is not uncommon for a patient to develop several foci of bone involvement over a period of years, only to have the disease disappear eventually.

The results for the disseminated form of the disease are somewhat different. The prognosis for these patients is primarily dependent on their age, the presence of organ dysfunction, and the response to therapy (see Fig. 32-17).[95]

Multiple chemotherapeutic agents have been used for the disseminated form of the disease, with response rates varying from 30% to 60%, of which about one half are complete responses.[193] Vincristine, vinblastine, cyclophosphamide, chlorambucil, methotrexate, and 6-mercaptopurine are all effective, as is the combination of prednisone with any of the preceding drugs. Patients with only multifocal bone disease usually survive, even when they do not initially reach a complete remission. Patients in the "poor-risk" category are less responsive to treatment and often die within a short period of time, even with multiple different chemotherapeutic regimens. Low-dose total-body or hemibody irradiation has also been tried in these patients.[62]

For those patients who survive solitary bony lesions, there are virtually no long-term sequelae of treatment unless the primary lesion has affected the hypothalamic–pituitary axis, although an occasional untreated vertebral lesion may result in permanent neurologic sequelae. Also, soft tissue lesions may produce a considerable amount of fibrosis when they heal, out of proportion to the radiation dose used, and even without being treated with radiation therapy. This is certainly true of those patients who have more disseminated disease, since almost half have long-term sequelae (unrelated to treatment), such as permanent diabetes insipidus, chronic lung disease, orthopedic disability, neurologic defects, emotional problems, intellectual impairment, and deficits in hearing.[96] Thus, even though the chances of survival are good for most patients, the disability due to the disease remains high.

Hemangiomas and Vascular Malformations

It has been estimated that 10% of all children born are afflicted with a hemangioma, and since 30% occur in the head and neck, it is the most common pediatric neoplasm arising in the head and neck.[4,80] There are numerous methods of classification suggested in the literature, the most common one being a division into capillary, cavernous, and juvenile. A more practical and simpler classification has been proposed by Mulliken and Glowacki.[133] They divided hemangiomas into two types: (1) those exhibiting a history of rapid neonatal growth and slow involution, characterized by hypercellularity during the proliferating phase (*hemangiomas*), and (2) those present at birth that grow commensurately with the child and are characterized by a normal rate of endothelial cell turnover (*malformations*). In other words, the term *hemangioma* was proposed to be limited to those lesions that show increased mitotic activity. Hemangiomas were present at birth only as a small red mark in 40% of the patients in this series and appeared after birth in the rest. The lesions usually grew rapidly for 6 to 8 months, then regressed. They could be superficial or deep lesions or a combination of both.[133] Radiographically, hemangiomas are distinguished by a well-circumscribed soft tissue mass on roentgenograms and angiograms, with the presence of intense, persistent tissue staining on the latter, usually organized in a lobular pattern. As the lesions involute, the staining becomes less intense. Direct arteriovenous shunting is not usual (Fig. 32-18).[19]

In the series reported by Mulliken and Glowacki[133] and Burrows and coworkers,[19] vascular *malformations*

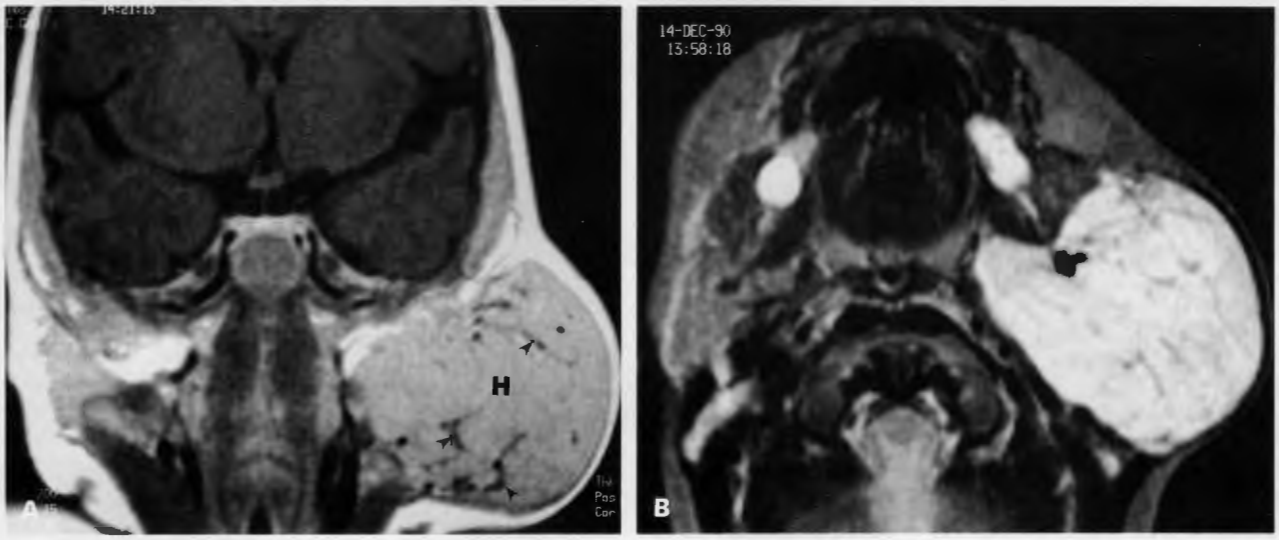

Figure 32-18. An infant had a parotid region mass. The appearance is most consistent with a juvenile, proliferative hemangioma. (*A*) Coronal contrast-enhanced T1-weighted MRI shows a homogenously enhanced hemangioma (H) in the parotid space with some enlarged vessels (*arrowheads*). (*B*) T2-weighted axial MRI shows the very bright signal of this lesion due to the many dilated vascular spaces containing slow-flowing blood.

were present at birth in 90% of patients and grew at the same rate as the child. These lesions did not regress and had various combinations of capillary, venous, and arterial components, with or without fistulas.

On plain roentgenograms, malformations appear as diffuse soft tissue masses with loss of normal tissue planes. Phleboliths (soft tissue calcifications) are often present. Angiography reveals large, dilated vascular spaces that fill in the venous phase and produce extended pooling of contrast material. Tissue staining is faint or absent.[19]

There are lesions that are a combination of a hemangioma and a malformation and others that also have a lymphatic component.

Whereas most hemangiomas present as a single entity, there is a group of diseases that produce diffuse angiomatosis in infants. Sturge–Weber syndrome (encephalotrigeminal syndrome, encephalofacial angiomatosis) is a triad with a cutaneous hemangioma in the distribution of the trigeminal nerve, a homolateral meningeal hemangioma causing calcification and neurologic signs, and choroidal hemangioma that sometimes causes glaucoma. Incomplete forms of the syndrome are more common than the complete triad. Von Hippel–Lindau disease consists of hemangiomatosis of the retina and cerebellum. Maffucci's syndrome (dyschondroplasia) represents hemangiomatosis of the skeletal system.

Although most hemangiomas undergo spontaneous involution, this may take as long as 4 to 7 years to occur.[11,65,112] If the lesion is not causing functional impairment, then simple observation is adequate, at least until school age, when treatment may be considered if there is no regression.[65]

There are certain lesions, however, that may require immediate intervention, such as subglottic hemangiomas, eyelid hemangiomas, and those occurring in the lip, nose, tongue, or pharynx, where permanent functional impairment may result. Subglottic hemangiomas may be life threatening. These lesions are usually located immediately below the vocal cords in the child; they are sessile and not well demarcated from the surrounding structures, with mucosa usually covering the mass and obscuring the usual red color of a hemangioma.[21,51] Subglottic hemangiomas occur more often in girls, who usually present with stridor. With small lesions, observation (with or without tracheotomy) may be safe, but most lesions will usually require early intervention.

Orbital hemangiomas, although less acute in their symptoms, may also need intervention rather than observation if they are large enough to cause proptosis and diplopia or otherwise interfere with vision; lack of the use of one eye in early childhood will prevent normal visual development.

When the decision to intervene therapeutically is made, for either cosmetic or functional reasons, surgical excision is the treatment of choice for small lesions. Surgical therapy for the more extensive lesions, however, may result in severe hemorrhage, and perhaps even airway obstruction with oral cavity and subglottic lesions. Large resections of defects on the face may give poor cosmetic results, even with good skin grafting. In these settings, corticosteroids are recommended by many authors.[35,45,53,65] Doses of 20 to 40 mg of prednisone for 3 to 21 days can cause rapid cessation of growth and even involution of the lesions at times. This works primarily on hemangiomas (as defined by Mulliken and Glowacki[133]) and less well on malformations.

For lesions unresponsive to corticosteroids there are several alternatives. Carbon dioxide laser has been reported to be successful in the treatment of some subglottic and intraoral hemangiomas.[69] There is minimal bleeding and a lack of postoperative edema reported with this technique, and it is usually successful in patients in whom other treatment has failed. It is not recommended, however, for deep lesions with large vessels. The argon laser has also been advocated of late for extensive superficial hemangiomas.[140] Sometimes there is extensive scarring with this technique, and there is often a

need for multiple treatments. Percutaneous embolization and sclerosing therapy for large hemangiomas and vascular malformations has been performed with some success.[113] This is frequently used as an adjunct to surgery or as definitive therapy, with increasing success as endovascular therapeutic techniques have improved over the past several years (see Chap. 4).

Interferon alfa-2a has recently been reported to produce regression of hemangiomas, lymphangiomas, and associated disorders. Ezekowitz and associates[50] reported the results for 20 infants with life-threatening hemangiomas treated with daily subcutaneous injections of interferon alfa-2a after they had failed to respond to corticosteroid therapy. Eighteen of the lesions responded with 50% to 100% regression. Transient side effects included fever in all patients, transient neutropenia in one patient, and a superficial skin slough in one patient.

In the past, a large number of hemangiomas were treated with radiation therapy, particularly those causing acute symptoms such as eyelid, orbital, or subglottic lesions. Malformations do not respond so well. The results of radiation therapy for hemangiomas are initially satisfactory, with a decrease in the size and cosmetic deformity of the mass in most patients, although such a change may take 2 months to a year to be complete. Doses in the range of 200 cGy in one fraction to 450 cGy in three fractions have been recommended.[185] The main problem with radiation therapy is the carcinogenic potential. In one review from Li and coworkers of 4746 patients treated in infancy for hemangioma of the skin at the Children's Hospital Medical Center in Boston from 1946 to 1968, only three cancer deaths were found (vs. 2.4 expected), with follow-ups of 6 to 28 years.[107] Only one tumor was in proximity to the treatment field. Therefore, external-beam irradiation may be a viable alternative for patients with lesions not easily amenable to other approaches. Electrons may be used to decrease the dose to underlying tissues.

Lymphangioma

Lymphangiomas are considered by most authors to be congenital malformations rather than neoplasms.[197] There are three types: (1) *lymphangioma simplex*, which has many thin-walled channels; (2) *cavernous lymphangioma*, which has larger cystic areas within a fibrous adventitia; and (3) *cystic hygroma*, a lesion of large, multiple cystic spaces of different sizes. The former two are more common in the oral cavity and orbit, while cystic hygroma occurs in the neck. None of the lesions is encapsulated; all send microscopic extensions into surrounding tissues. Most lesions are diagnosed early in life, often in the first year, but a few may go unnoticed for many years.

The exact origin of lymphangiomas is controversial. Sabin's "centrifugal" theory proposes endothelial sprouts propagating outward from primordial sacs to form the peripheral lymphatic system. The "centripetal" theory of McClure and Huntington proposes the development of peripheral lymphatics from mesenchymal slits in sequestered portions of the primordial sacs. Failure of these sequestrations to ultimately join the venous system results in the formation of a cystic hygroma.[15] The posterior triangle is the most common site.[91] The overlying skin is usually not affected. Size fluctuations often occur with upper respiratory tract infections.

Neck lesions are usually soft, cystic masses that transilluminate and often cause respiratory compromise. Oral cavity lymphangiomas can occur submucosally, making diagnosis difficult. Orbital lesions usually have lid or conjunctival involvement with the appearance of typical dilated vascular channels into which hemorrhage may occur. Proptosis is the most common symptom. CT and MRI studies can help determine the extent of the lesion, with a characteristic appearance of a multiloculated cystic mass with smooth septa of variable thickness.[114] MRI maps the soft-tissue extent most precisely, and CT may be used to show the precise effect on surrounding bones. Contrast studies may be used for both MRI and CT to differentiate the lymphangiomatous from the frequently admixed hemangiomatous component of the lesion (Fig. 32-19).

Surgical excision is the treatment of choice, although aspiration may serve as a temporizing measure. Laser marsupialization can be used for laryngeal or oral lesions.[15,34]

As the affected child grows, so does the lymphangioma. Some lesions may spontaneously regress, but most authors consider the typical course to be one of progression. Thus, there is controversy as to whether it is preferable in young children to treat the patient immediately after diagnosis or to wait until the child is older and can better withstand surgery. Few lymphangiomas can be totally removed in one operation, and staged resections may be necessary. In a series of 137 patients, Brock and coworkers[15] reported only a 6% recurrence rate after a complete surgical resection; with known subtotal resection, the recurrence rate was 35%. There is no purpose served by removing important normal structures because partial excision may cause enough scarring to prevent recurrence.

Figure 32-19. Contrast-enhanced CT of a child with a very extensive lymphangioma (L) of the face, parotid spaces, prestyloid parapharyngeal space, and floor of the mouth.

Radiation therapy has been used in lymphangiomas, and although it is considered to be of little value by most authors, it occasionally will provide a good response.[163] Our own experience is that a dose of 2000 to 3000 cGy at 160 to 180 cGy per day is required.

Teratomas

Teratomas have been reported in most midline structures, and the head and neck is not without its representation. A teratoma will be present in the head and neck in about 1 in 40,000 births.[78] They are thought to be derived from pluripotential cells, and since they can grow independent of the host they are usually considered true neoplasms.

The functional classification of these tumors was proposed by Arnold[2] in 1888 and has been accepted by many authors. The two most common types are the dermoids and the true teratomas. The dermoids constitute the majority of the group and are bigerminal, being composed of epidermal and mesodermal elements. They usually consist of an epithelial-lined cavity with variable numbers of skin appendages such as hair and sebaceous glands. Most arise from the midline region of the nasopharynx and are not associated with cranial abnormalities.[20,58] They also may occur in the orbit and midline and tip of the nose, as well as in the oral cavity. The true teratomas are trigerminal. Sometimes they differentiate to the degree that organs can be recognized histologically. They are associated with developmental abnormalities of the skull and are usually based in the nasopharyngeal vault, but they may also arise in the neck, orbit, or oral cavity (Fig. 32-20).[75]

Most of these children present with respiratory obstruction, often at birth or shortly thereafter. The differential diagnosis includes cystic hygroma, congenital goiter, thyroglossal duct cyst, branchial cleft cyst, arteriovenous malformation, lipoma, and laryngocele.[194] These are simply differentiated by CT or MRI. Prenatal ultrasound can be valuable to identify fetuses at risk for possible airway obstruction and to have an airway management team ready at birth.[76,77,90] The primary treatment is surgical, and for the most common tumor, the dermoid, the prognosis is excellent. The local recurrence rate is small, even only with avulsion of the tumor.[20]

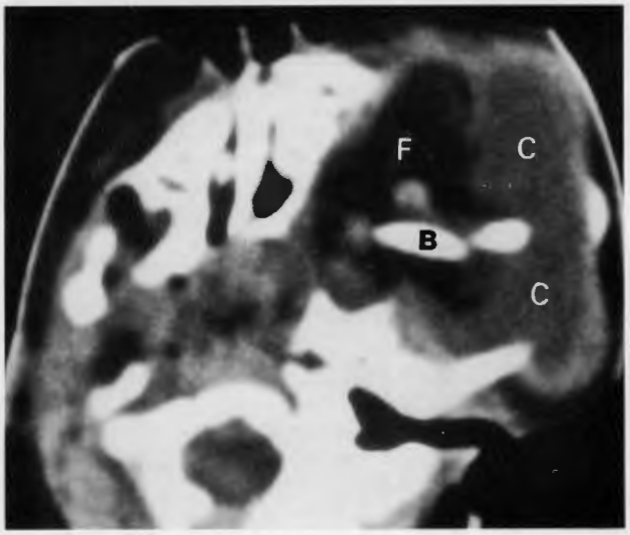

Figure 32-20. CT of an infant with a teratoma. Fatty (F), cystic (C), and bony (B) components are all readily identified.

True teratomas have a less favorable prognosis. Jordan and Gauderer have proposed a classification system based on birth status, age at diagnosis, and the presence of respiratory distress. Group I (stillborn and moribund live newborns) had a mortality rate of 100%, group II (newborns with respiratory distress) had a mortality rate of 43.3%, group III (newborns without respiratory distress) had a mortality rate of 2.7%, group IV (children aged 1 month to 18 years) had a mortality rate of 3.2%, and group V, adults, had a mortality rate of 43.5%. They noted that prenatal ultrasound should aid survival in group II patients.[87]

Cervical teratomas presenting in adulthood have an aggressive metastatic potential, while metastasis from childhood teratomas is rare, although it has been reported.[144,191]

COMPLICATIONS OF TREATMENT

Besides the usual risks and sequelae involved in treating head and neck cancers, which are discussed elsewhere in this book, the developing child has additional risks from both radiation therapy and chemotherapy. The sequelae of radiation therapy are better known because the modality has been in use for a longer period of time, but the risks attendant with giving cytotoxic drugs are also beginning to be recognized.

Radiation Therapy

Bone and Soft Tissues

There is adequate evidence that radiation doses in the range of 2000 cGy or less can slow bone growth in children, and doses above this range will usually close epiphyses and completely halt bone development.[70,138,161] Obviously, the younger the age at the time of treatment, the greater the resulting deformity. In the teenage years, when the development of the skull and facial bones is virtually complete, there is little noticeable deformity, but for children in the first decade and particularly for infants, radiation in the range of 2000 cGy or more can result in permanent abnormal bony development (see Fig. 32-11*C* and *D*).

The development of soft tissues such as muscles is affected by similar doses. Hypoplasia of the soft tissues within the treatment field is usual with doses above 2000 cGy.

Teeth

The developing teeth are also sensitive to radiation in therapeutic doses, with doses as low as 1800 to 2000 cGy producing a high incidence of complications.[172] Sequelae in permanent teeth after radiation therapy in infancy include retarded root structures, dwarfed teeth, and occasionally failure of one or more permanent teeth to form.[93] Sometimes, permanent teeth may erupt early or may calcify prematurely.[16,175]

Salivary Glands

Radiation clearly damages salivary function. In a study of 20 children treated for sarcomas of the head and neck, Fromm and associates[55] found that 40% of the children treated with more than 4000 cGy had absent parotid secretions. No apparent dysfunction occurred in children treated with less than 4000 cGy. It is important to consider this in planning radiation therapy, since lack of parotid secretions causes dryness of the mouth, taste abnormalities, and dental caries.

Eyes

It is not clear whether children's eyes are more sensitive to radiation than the eyes of adults. A considerable number of children have been treated to the whole eye at various institutions for retinoblastoma with doses of 3500 to 5000 cGy or above. Good vision is preserved in the majority of patients who received these doses if they had a small tumor at the time of treatment. There may be a slightly better chance of preserving good vision if the dose is kept below 4000 cGy.[26] Data from treating orbital rhabdomyosarcomas to 5000 to 6000 cGy without chemotherapy show that only a few patients retained useful vision.[74] Thus, it appears that doses up to 4500 cGy are probably tolerated fairly well by the eye of a child, even an infant, but doses of 5000 cGy and above are poorly tolerated. The additive effect of chemotherapy may increase the risk of permanent damage at any given dose level.

The most common cause of blindness is retinal or optic nerve damage, just as in adults. Most patients with orbital tumors usually receive high doses to the lens as well as the retina, and the incidence of cataracts in children at doses of 5000 cGy or above appears to be close to 100%.[164] (See Chapter 13 for a full discussion.)

Central Nervous System

Although in most head and neck cancers (excluding brain tumors) little radiation is delivered to the brain parenchyma itself, in parameningeal rhabdomyosarcoma a considerable amount of brain tissue receives high-dose irradiation. With the doses used (up to 5500 to 6000 cGy), brain necrosis is rare. There is no evidence that the risk of myelitis is different in children than in adults, but the addition of intrathecal chemotherapy to only 3000 cGy of cranial and spinal irradiation produced a high rate of myelitis (3.4%) in the children with parameningeal rhabdomyosarcomas treated in the Intergroup Rhabdomyosarcoma Study between 1977 and 1987.[150]

Disturbances of the hypothalamic–pituitary axis are more common. Neuroendocrine abnormalities after treatment are known to be dose-dependent. The most sensitive neuroendocrine function is growth hormone production; doses of less than 1800 cGy may cause growth hormone deficiencies.[167] Not all patients with growth hormone deficiencies have decreased stature. (See Chapter 13.)

Chemotherapy

The most common drugs used in treating cancers that occur in the head and neck in children are vincristine, doxorubicin, dactinomycin, cyclophosphamide, and methotrexate. Each has its own risks and side effects, most of which are similar in children to the side effects in adults and are discussed in Chapter 7.

Second Malignancies

One of the most serious sequelae of cancer treatment in children is the development of a second neoplasm. Although irradiation has been known for a long time to produce a risk of oncogenesis, it is now becoming clear that chemotherapy has similar risks (Table 32-9).[106,126,127,189] In adults, there are good data regarding the risks of certain chemotherapeutic drugs and the development of a second malignancy. Alkylating agents have been implicated in causing acute myelogenous leukemia.[46,157] Nitrogen mustard and procarbazine are believed to induce leukemia in patients treated for Hodgkin's disease, especially in combination with radiation.[97,190]

TABLE 32-9. Etiology of Second Malignant Neoplasms (308 Patients)

Site of Origin	No. of Patients	Radiation Associated	No Radiation Therapy	
			Total	Chemotherapy
Bone sarcomas	67	52	15	8
Soft tissue sarcomas	59	43	16	6
Leukemia/lymphoma	59*	36	23	12
Skin cancers	31†	19	11	5
Brain tumors	29†	13	15	11
Thyroid tumors	26	24	2	1
Breast cancer	13	9	4	0
Other neoplasms	24	12	12	6

* Two patients in this group with unknown radiation therapy history.

† One patient in this group with unknown radiation therapy history.

(Meadaws AT, Baum E, Fossati-Bellani F, Green D, Jenkin RDT, Marsden B, Nesbit M, Newton W, Oberlin O, Sallan SG, Siegel S, Strong LC, Voute PA. Second malignant neoplasms in children: an update from the Late Effects Study Group. J Clin Oncol 1985;3:534)

In children, alkylating agents have also been implicated in the causation of secondary bone cancer and other secondary neoplasia. In a report from the Late Effects Study Group, Tucker and coworkers[192] found an increased incidence (4.8 to 8.5 times expected) of secondary bone tumors with the use of alkylating agents (in nonirradiated patients) in the treatment of the initial tumor. The use of radiation therapy (more than 1000 cGy) with alkylating agents yielded an increased risk 14.2 to 59.4 times than expected, depending on the doses of alkylating agents used. De Vathaire and coworkers[42] found an increased risk of all secondary tumors after the use of alkylating agents in the treatment of childhood cancers. The combination of radiation therapy and an alkylating agent has been shown to produce a higher risk than either modality alone.

Not only does the treatment of childhood cancer give rise to secondary oncogenesis, it also appears that many children who develop one childhood cancer have a higher risk of developing a second cancer at a later time, even without irradiation or chemotherapy (see Table 32-9).[126,128] In addition, many of the tumors that arise in the field of irradiation occur in patients known to have a genetic susceptibility to developing second cancers, such as patients with bilateral retinoblastoma. The incidence of second tumors begins to rise within 5 years after therapy, and the incidence continues to rise for many years after that, whether the tumor is induced by treatment or inherent in the child.[192]

In 1990 it was estimated that one of each thousand adults was a survivor of childhood cancer.[128] Many of the effects of therapy on the long-term quality of their lives are still unknown.

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33

ADULT MESENCHYMAL TUMORS PRESENTING IN THE HEAD AND NECK

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In general, mesenchymal lesions in the head and neck behave as do their counterparts in the extremities. All of the tumors described in this chapter, however, are uncommon, and some are rare. It is important to diagnose them correctly and to apply the proper treatment since almost all of them are potentially curable. Mesenchymal tumors occurring mostly in children are discussed in Chapter 32.

BONE AND CARTILAGE TUMORS

Aneurysmal Bone Cyst

An aneurysmal bone cyst is not a true neoplasm but rather a benign bone lesion of unknown etiology. It has been postulated that it may be caused by a local circulatory disturbance with resultant increased venous pressure and may arise either alone or in conjunction with other lesions such as giant cell tumor, chondroblastoma, or fibrous dysplasia. It is half as common as giant cell tumor of bone, it occurs with a slight female preponderance, and roughly 80% of patients are younger than 20 years of age at the time of diagnosis. Bones of the head and neck are affected in about 13% of cases, usually involving either the calvarium or cervical vertebrae. The patient generally presents with a painful mass that, roentgenographically, appears as an eccentric zone of expanded rarefied bone with a peripheral eggshell-thin rim of subperiosteal new bone.[11,23,50,52] Cervical spine lesions often cause neurologic symptoms.

Surgery has generally been accepted as the treatment of choice and may entail either curettage or en bloc resection. Recurrence rates after curettage vary from 21% to 44% and increase with incomplete resection, lesions that are greater than 5 cm, and age younger than 15 years.[65,79] The recurrence rate after en bloc resection is essentially zero. Radiation therapy is usually reserved for surgically inaccessible or recurrent lesions and is successful in 80% to 90% of cases.[59,65,79] Doses in the range of 2000 to 3000 cGy in 3 to 4 weeks are adequate with megavoltage (Marcus RB, Jr, unpublished University of Florida data, April 1992).[59] The response to radiation therapy is generally immediate, with symptoms resolving within a few days of the initiation of treatment. Healing of the involved bone may begin by the end of treatment, but complete healing takes an average of 4 to 8 months (Fig. 33-1) (Marcus RB, Jr, unpublished University of Florida data, April 1992).[59]

Giant Cell Tumor

Giant cell tumor of bone is also of unknown etiology and involves the head and neck in about 3% of cases.[23] It occurs with a slight female preponderance, especially in younger patients; 85% of patients are older than 20 years of age.[52] The tumor usually occurs in the epiphysis and metaphysis of the long bones after closure of the growth plate; when the head and neck area is involved, however, the most common site is the sphenoid or cervical spine. If the tumor occurs in association with Paget's disease, there is a tendency for involvement of the calvarium and facial bones.[52] The patient generally presents with a painful mass that, roentgenographically, appears as an expanded zone of radiolucency with an indistinct margin; periosteal new bone formation is almost never present.[23]

There is controversy as to whether histologic grading is of prognostic value, although there is agreement that even cytologically benign giant cell tumors may develop metastases in less than 1% of cases.[23,52] To make matters worse, giant cell tumor may be confused histologically with nonossifying fibroma, chondroblastoma, chondro-

Figure 33-1. A 15-year-old boy had an aneurysmal bone cyst of the C2 vertebra. (*A*) Roentgenograms of the cervical spine obtained before treatment revealed a lytic lesion of the body of C2 with ballooning of the vertebral body anteriorly. The patient received 2829 cGy tumor dose in 14 fractions with 2-MV x-rays. At the time of his first follow-up visit 1 month after treatment, he had noted complete resolution of his neck pain. (*B*) Follow-up roentgenogram 3 months after treatment showed little change. (*C*) Over the next 4 months, almost complete ossification occurred. (*D*) Roentgenogram of the lesion 13 years after treatment shows residual abnormality but little change from appearance in *C*.

myxoid fibroma, giant cell reparative granuloma, aneurysmal bone cyst, hyperparathyroidism, and osteosarcoma. About 10% of cases may undergo malignant transformation; and when this occurs, it is associated with an 80% mortality rate.[23]

Evaluation may include an angiogram, which often shows a hypervascular mass with an intense, nonhomogeneous capillary blush.[52] Angiography is usually not necessary if a careful imaging has been completed, and the extent of the mass is often best seen on computed tomography (CT) or magnetic resonance imaging (MRI) (Figs. 33-2 and 33-3).

Surgery is regarded as the treatment of choice and entails either curettage or en bloc resection. Curettage is associated with a local recurrence rate of roughly 50%.[23] Cryosurgery or cementation will decrease the rate of local recurrence to less than 10%, and local recurrence after en bloc excision is noted in less than 5% of cases.[68]

Radiation therapy is usually reserved for lesions that are incompletely excised, recurrent, or unresectable. It may achieve local control, and thus long-term cure, in over 80% of cases with doses in the range of 3500 to 4800 cGy.[18,42,83] At the University of Florida, 4500 cGy at 180 cGy per day is the recommended fractionation.[7] Irradiation may be more successful in tumors arising from membranous bones as opposed to those arising from long bones.[7,30] The response of giant cell tumors to irradiation can be strikingly different from that of aneurys-

mal bone cysts (see Fig. 33-3). Although one series reported that 62% of patients may develop pain relief before the end of therapy, in some patients pain may not be completely relieved for a period of months to a year or more and, occasionally, may worsen right after the completion of radiation therapy. Little improvement is noted on roentgenograms for months. In fact, shortly after the end of treatment, absorption of the rarified rim of new bone may occur, causing great concern. Within 6 months the mass should begin to shrink, with new bone formation around the periphery. There is rarely complete resolution of the mass, and maximum shrinkage and ossification may require 1 or 2 years.

The most common site of metastases for giant cell tumor is the lungs, although the incidence is low.[7,10,74] If the metastases are few, the treatment of choice is surgical resection with close follow-up. Long-term survivors have been reported using this approach.[10,74] With a large number of lesions, surgery is not as useful. Some patients have been reported to respond and perhaps even be cured with chemotherapy. In the University of Florida experience, six patients with lung metastases received a variety of chemotherapy agents, including doxorubicin (Adriamycin), cyclophosphamide (Cytoxan), melphalan (Alkeran), and dacarbazine (DTIC), and we have seen two complete responses and one partial response in the five patients. The two patients with complete responses are long-term survivors.[10] One patient who did not respond to chemotherapy was treated with 1600 cGy whole-lung irradiation, with a boost to 3500 cGy to one large left lower lobe lesion. This produced a complete response, although a single lesion recurred later in the right lung 2 years after treatment. This has been salvaged to date with an additional course of localized irradiation. Occasionally, lung metastases from giant cell tumors have an unpredictable course, and some have been observed to remain stable for many years and never become a threat to the patient's life.

Chordoma

Chordoma is a tumor that arises from remnants of the primitive notochord.[23,52] It occurs almost exclusively along the axial skeleton, with 36% of cases in the base of the skull and 7% in the cervical spine.[23] There is a slight

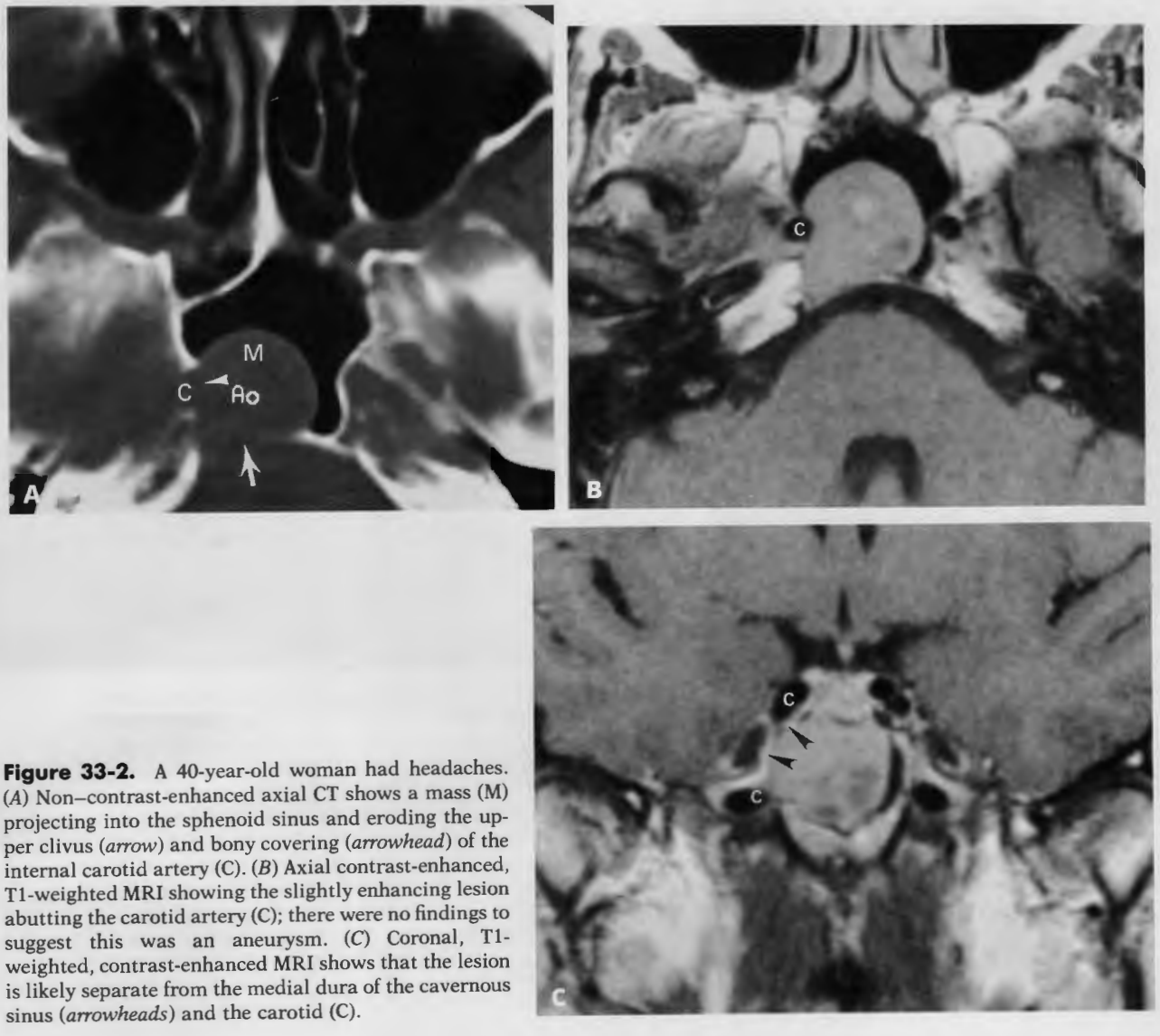

Figure 33-2. A 40-year-old woman had headaches. (*A*) Non–contrast-enhanced axial CT shows a mass (M) projecting into the sphenoid sinus and eroding the upper clivus (*arrow*) and bony covering (*arrowhead*) of the internal carotid artery (C). (*B*) Axial contrast-enhanced, T1-weighted MRI showing the slightly enhancing lesion abutting the carotid artery (C); there were no findings to suggest this was an aneurysm. (*C*) Coronal, T1-weighted, contrast-enhanced MRI shows that the lesion is likely separate from the medial dura of the cavernous sinus (*arrowheads*) and the carotid (C).

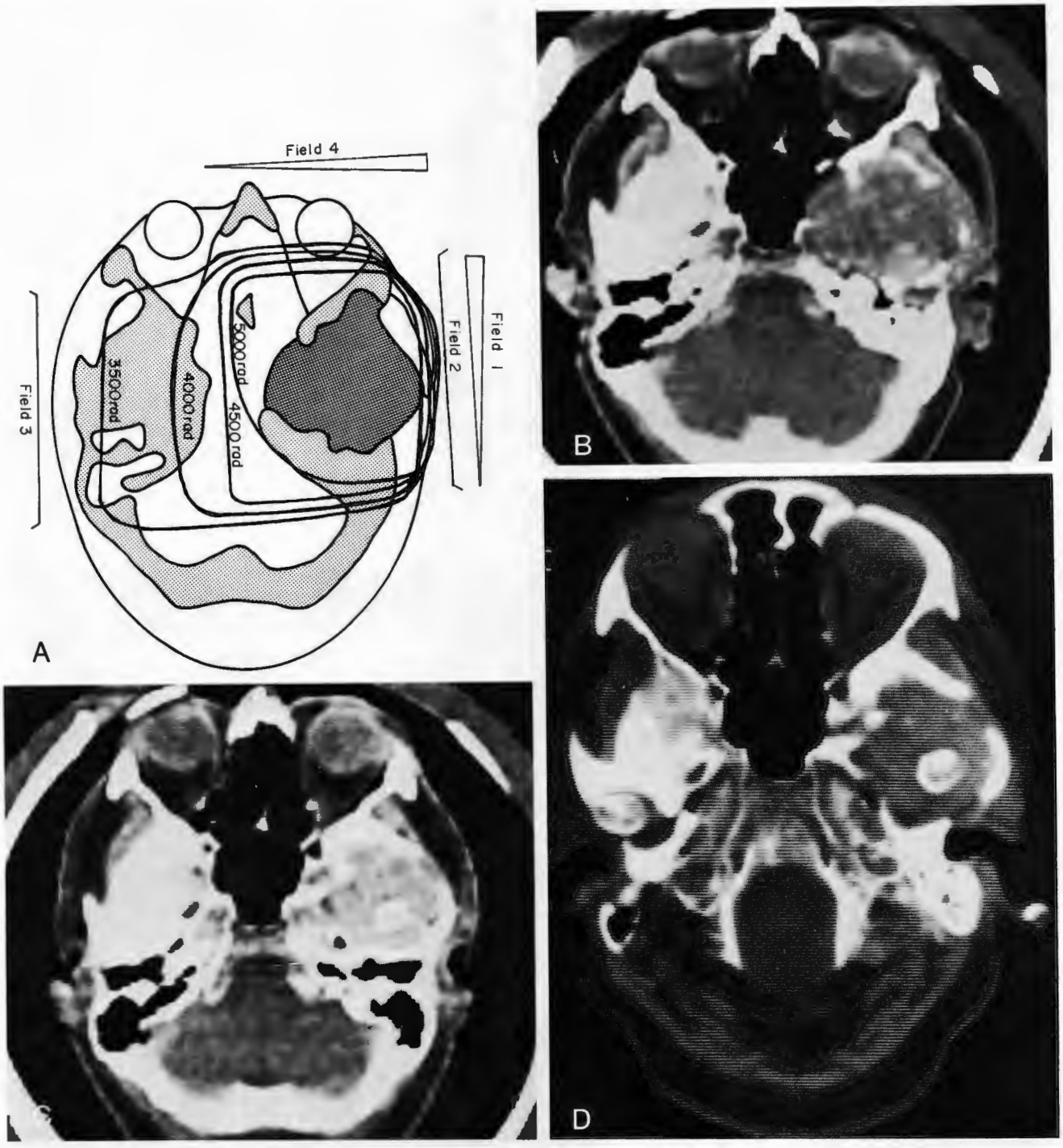

Figure 33-3. A 75-year-old man had a giant cell tumor of the right temporal bone. On physical examination, he was also noted to have a 10-cm mass overlying the right temporal bone. Initial CT of the head done in September 1979 (not shown) revealed a large mass of the right infratemporal and temporal fossa, extending superiorly 2 cm above the level of the optic chiasm, medially to the sphenoid sinus, and anteriorly to the posterior aspect of the orbit. (*A*) The patient received 5000 cGy external-beam irradiation using ^{60}Co and 17-MV x-rays. During the initial 2 weeks of treatment, the patient noted a prompt decrease in the size of the right temporal bulge. At the completion of radiation therapy he noted a modest improvement of his previously noted right facial nerve palsy. The tumor mass is represented by the dark stippled area. (*B*) Follow-up CT at 5 months revealed 20% to 30% decrease in size of the mass as compared with his pretreatment scan. (*C*) Repeat CT at 21 months revealed continuous regression of the mass and reossification of the involved bones. (*D*) CT at 33 months showed no further change. The patient remained without evidence of recurrence at 12 years.

male preponderance.[46] The average age at diagnosis for head and neck lesions is 38 years, with a range of 8 to 75 years.[46] This is about 10 years less than the reported average age of 48 years for chordoma in general.

The tumor is slow growing, and symptoms are usually present from 6 months to 3 years before diagnosis.[46] Symptoms from tumor arising in the basisphenoid will depend on its route of spread, which may be intracranially or inferiorly into the nasopharynx, nasal cavity, and maxillary sinus. Patients commonly present with visual disturbances such as diplopia (secondary to involvement of the abducens nerve) or visual field deficits. In addition, they may present with headache, nasal obstruction, ear pain, or proptosis. Cervical chordoma may present as a painful mass in the lateral neck or pharyngeal wall associated with cranial nerve deficits or symptoms of spinal cord compression (Fig. 33-4). About 10% of patients present with or develop distant metastasis, usually to the lungs.

Roentgenographically, the lesion appears as an expansile, osteolytic lesion, sometimes with areas of calcification, often associated with a soft tissue mass.[23,46] Usually, both CT and MRI are needed to fully define the extent of the lesion. The lesions are characteristically bright on heavily T2-weighted MRI studies; this can be a helpful point in the differential diagnosis of skull base lesions (see Fig. 33-4).[57]

Treatment of chordoma entails complete resection, when feasible, radiation therapy, or both of these modalities. Complete excision is rarely possible for head and neck chordoma because of the inaccessible location, although one long disease-free survival has been reported after resection alone.[92]

The results of treatment with radiation alone or radiation plus surgery are poor.[20,46,47,69,70,82,92] Treatment is followed by local recurrence in over 80% of cases within 5 years of treatment and is fatal within a time period varying from weeks to several decades.[20]

Series of patients with clival chordomas and chondrosarcomas of the cervical spine treated at Massachusetts General Hospital and the University of California at San Francisco using x-rays and protons or helium ions have

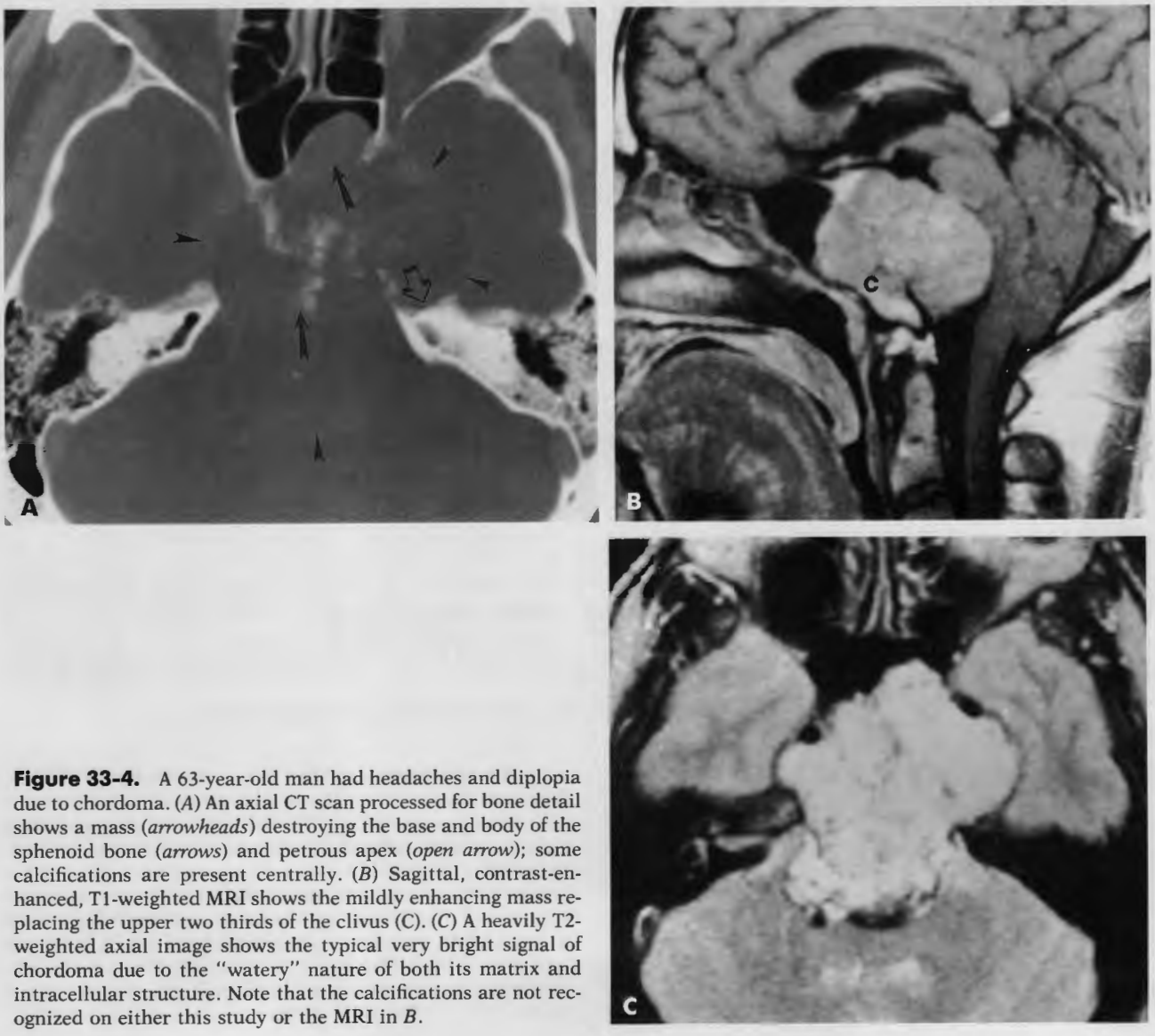

Figure 33-4. A 63-year-old man had headaches and diplopia due to chordoma. (*A*) An axial CT scan processed for bone detail shows a mass (*arrowheads*) destroying the base and body of the sphenoid bone (*arrows*) and petrous apex (*open arrow*); some calcifications are present centrally. (*B*) Sagittal, contrast-enhanced, T1-weighted MRI shows the mildly enhancing mass replacing the upper two thirds of the clivus (C). (*C*) A heavily T2-weighted axial image shows the typical very bright signal of chordoma due to the "watery" nature of both its matrix and intracellular structure. Note that the calcifications are not recognized on either this study or the MRI in *B*.

yielded better results. The Massachusetts General Hospital series, which did not report chordoma and chondrosarcoma separately, reported a probability of local control of 82% at 5 years and 58% at 10 years. The probability of disease-free survival was 76% at 5 years and 53% at 10 years. Only 11 patients had follow-up for longer than 5 years.[1] The California series reported a probability of local control at 5 years of 55% for chordoma. The probability of survival at 5 years was 50%.[8] The primary risk with particle beam treatment appears to be damage to the visual apparatus, with three patients in each series developing visual complications, including two patients with total blindness. Although the number of patients is relatively small and the follow-up period is relatively short in both series, combinations of particle beams and photons are probably the treatment of choice for most clival chordomas.

Chondrosarcoma

About 5% of chondrosarcomas occur in the head and neck. Most lesions are primary, but chondrosarcomas may arise in a multitude of preexisting conditions, including enchondroma, exostosis, juxtacortical chondroma, Maffucci's syndrome, chondromyxoid fibroma, chondroblastoma, and irradiated bone. Roentgenograms show bone destruction with amounts of chondroid matrix calcification varying from none to extensive.

The most common sites of head and neck chondrosarcoma are the maxillofacial areas and the jaw. Cervical spine and laryngeal lesions also occur, but primary lesions of the skull are uncommon. Chondrosarcomas often have a progressive and ultimately fatal course of disease, but many patients survive for prolonged periods with multiple recurrences. Most die of failure to control local disease, followed by extension of tumor into the cranial cavity. An occasional patient dies of metastatic disease. The mandible appears to be a worse site for chondrosarcoma than the maxilla.[6]

The primary treatment for chondrosarcoma is surgical, and if an adequate resection can be done, the local control rate is good.[14,31] Lesions in the head and neck are often difficult to completely remove, particularly those in the maxillofacial region and in the cervical spine. Laryngeal lesions arise from the cricoid or thyroid cartilage.[34] Most laryngeal lesions are low grade and rarely metastasize, so that excision is usually adequate; a local recurrence can be treated with a laryngectomy (Fig. 33-5).[34,36]

Chondrosarcoma was once thought to be resistant to radiation therapy; considerable data, however, suggest otherwise. Harwood and coworkers reported 31 patients treated primarily with radiation therapy because the site was not suitable for excision.[43] Five of 11 patients with well-differentiated and moderately well-differentiated lesions, including two in the head and neck, remained without evidence of recurrence at 3½, 5, 5, 15, and 15 years after radiation therapy. The patients with high-grade lesions or secondary chondrosarcomas fared worse, with no controls beyond 1 year. There have been other reports of successful irradiation of head and neck chondrosarcoma.[67] Doses equivalent to those for a similar-sized squamous carcinoma should be used.

Series including patients with chordoma and chondrosarcoma of the cervical and base of skull region have been reported from Massachusetts General Hospital and the University of California at San Francisco. A combination of photons and protons or helium ions was used in most patients. The probabilities of local control and disease-free survival for the Massachusetts General Hospital series (including both chondrosarcoma and chordoma) were 82% and 59%, respectively. The University of California at San Francisco series reported probabilities at 5 years of local control and survival of 77% for chondrosarcoma patients. McNaney and coworkers reported three patients (excluding mesenchymal chondrosarcoma) who were treated with a combination of photons and neutrons; all were alive without evidence of local recurrence at 12, 26, and 30 months, although one had developed distant metastases.[61] Since chondrosarcomas may recur or metastasize as late as 10 years after therapy and only a small proportion of the patients in either series has had follow-up for longer than 5 years, additional follow-up is needed to confirm these results.

Figure 33-5. A 38-year-old man had hoarseness. Physical examination revealed a submucosal mass involving the aryepiglottic fold and true vocal cord with subglottic extension. Noncontrast-enhanced CT of the larynx was performed. At the false vocal cord level, the aryepiglottic fold is thickened by a calcified mass. The thyroid cartilage (*arrows*) is normal. The appearance of this mass was considered diagnostic of an enchondroma or low-grade chondrosarcoma; biopsy revealed low-grade chondrosarcoma. Because of the extensive cricoid cartilage involvement, the patient was treated with total laryngectomy.

Mesenchymal Chondrosarcoma

Mesenchymal chondrosarcoma is a distinctive type that occurs in both skeletal and extraskeletal forms and has a predilection for the facial bones and ribs. It is cellular, with many undifferentiated mesenchymal cells in which islands of relatively well-differentiated cartilage exist.[6] The lesions may recur after long periods of remission. Surgical excision and radiation therapy are effective for local control, but the cure rates are poor because of the rapid evolution of distant metastases. Although adjuvant chemotherapy is recommended by some (and is needed), effective regimens have yet to be discovered.[56(p1456)]

SOFT TISSUE TUMORS

Soft tissue tumors can be divided into low-grade neoplasms that may recur after inadequate excision but rarely metastasize and metastasizing soft tissue tumors that vary from low to high in grade.

Low-Grade, Rarely Metastasizing Lesions

Infiltrating Angiolipoma

Angiolipoma is a distinct neoplasm characterized by a predominance of blood vessels, infiltration of skeletal muscle, and the tendency to recur locally. It presents as a slow-growing soft tissue mass, which may be fixed to underlying structures. It is most common in the extremities, but it may occur in the neck and supraclavicular regions. It is often found to have infiltrated fascia, muscle, periosteum, and even bone, with complete disregard for anatomic barriers, although it rarely infiltrates nerves.[24,35]

Angiolipomas usually have their onset in the third and fourth decades of life, but they have been reported from infancy to late adulthood.[35,53]

On imaging studies, an infiltrating angiolipoma may show serpiginous structures overlying a diffuse background suggesting its fatty content. If the lesion is intramuscular, its various constituents may result in a heterogeneous appearance. The arteriographic appearance is distinctive, with hypervascularity, poor circumscription, vascular tufts, and tangled, enlarged draining veins.[19]

The lesion never metastasizes, but it has a tendency to recur locally. The treatment of choice is surgery; wide excision is necessary to prevent recurrence. Extensive resections are rarely indicated, but patients must be followed for long periods of time because late recurrence may occur. Radiation therapy has been used, but the results are inconclusive.

Pleomorphic Lipoma

A variant of lipoma has been described by Shmookler and Enzinger that can easily be confused with liposarcoma.[85] Histologically, most of the lesion is typical lipomatous tissue, but there are small atypical areas where floret-like, pleomorphic, multinucleated giant cells are common. The lesion occurs most commonly in the neck, where half of all cases present. Most patients are male, and the tumor is rare before the fifth decade of life. Most often an asymptomatic mass that has gradually enlarged over a period of several years is reported.

Treatment is surgical excision, and there was no evidence of local recurrence in any of the patients reported by Shmookler and Enzinger.[85]

Granular Cell Myoblastoma

Granular cell myoblastoma has an uncertain histogenesis and is found in nearly every tissue and organ. About 50% of these lesions occur in the head and neck. It is most common in the oral cavity, especially the tongue, but it may also occur in the neck, larynx, ear, lip, eyelid, orbit, and elsewhere. The average age at onset is in the fourth to fifth decade, but it has occasionally been reported in children.[88] Multiple lesions may occur in the same person.

Granular cell myoblastoma is considered a benign lesion, but it has been reported to become malignant and to metastasize, although not all pathologists recognize the existence of a malignant type.[6,40] The lesion may be confused with a squamous cell carcinoma if the biopsy specimen is shallow. Grossly, the lesion is usually small, not larger than 2 cm in most series. It is firm, elevated, plaque-like, and not encapsulated.[40] The rare malignant lesion tends to be larger and grow more rapidly.

Local excision is the treatment of choice. Radiation therapy may be of value for lesions unsuitable for surgical resection.

Aggressive Fibromatosis

Aggressive fibromatosis, first described by Macfarlane[55] in 1832, is a locally aggressive neoplasm of unknown etiology arising from musculoaponeurotic structures.[49,76] It may masquerade under many names (such as extraabdominal desmoid or fibrosarcoma grade 1, desmoid type) but should be approached as though it is a low-grade ("grade ½") fibrosarcoma. The entity is, however, distinct from low-grade fibrosarcoma in that there is no pseudocapsule formation and it does not metastasize. The benign histologic appearance is misleading, since the neoplasm penetrates fascial planes, implants easily along incisions and hematomas, and may invade bone. It may occur in any anatomic location, but it has a predilection for the shoulder girdle and the thigh.[28,94] It may occur at any age, although most tend to present in young adults.[49,94] There is a female preponderance in most series.[49]

The patient often presents with a history of a firm, slowly growing mass that, late in its course, may become fixed and painful.[28,76] The duration of symptoms may vary from months to several years but is usually about 6 months.[28]

Initial treatment is usually wide resection, which is followed by local recurrence in 27% to 57% of cases.[28,49] In situations in which a disabling or cosmetically deforming operative procedure is necessary to achieve a wide margin, irradiation alone is advised. There is no evidence to suggest that subtotal excision in this setting is of any benefit, and it may cause harm by complicating subsequent radiation treatment.[60]

Radiation therapy alone has been successful even in the treatment of large unresectable lesions. Radiation therapy is therefore used for inoperable or recurrent lesions, or after resection with narrow margins. It will achieve local control about 80% of the time (Fig. 33-6).[37,49,51,60,62,84,94] Recommended doses are in the range of 5000 to 6000 cGy at 180 cGy per fraction, five fractions per week. There is no notable dose–volume effect and no significant benefit reported in using doses of 6000 cGy or higher.[51,60,62,84,89] In addition, Sherman and associates reported that there were more serious complications with doses above 6000 cGy.[84]

The regression rate is slow, and gross disease may require 6 months to several years to shrink after successful radiation therapy (Fig. 33-7). Most local recurrences after radiation therapy are marginal failures on the edge of the radiation field.[51,60] CT and MRI are used to map the extent of the lesion. These imaging tests are not specific for this histology, although lesions with densely fibrous stroma *may* have signal intensities nearly that of skeletal muscle on heavily T2-weighted images (Fig. 33-8).[57]

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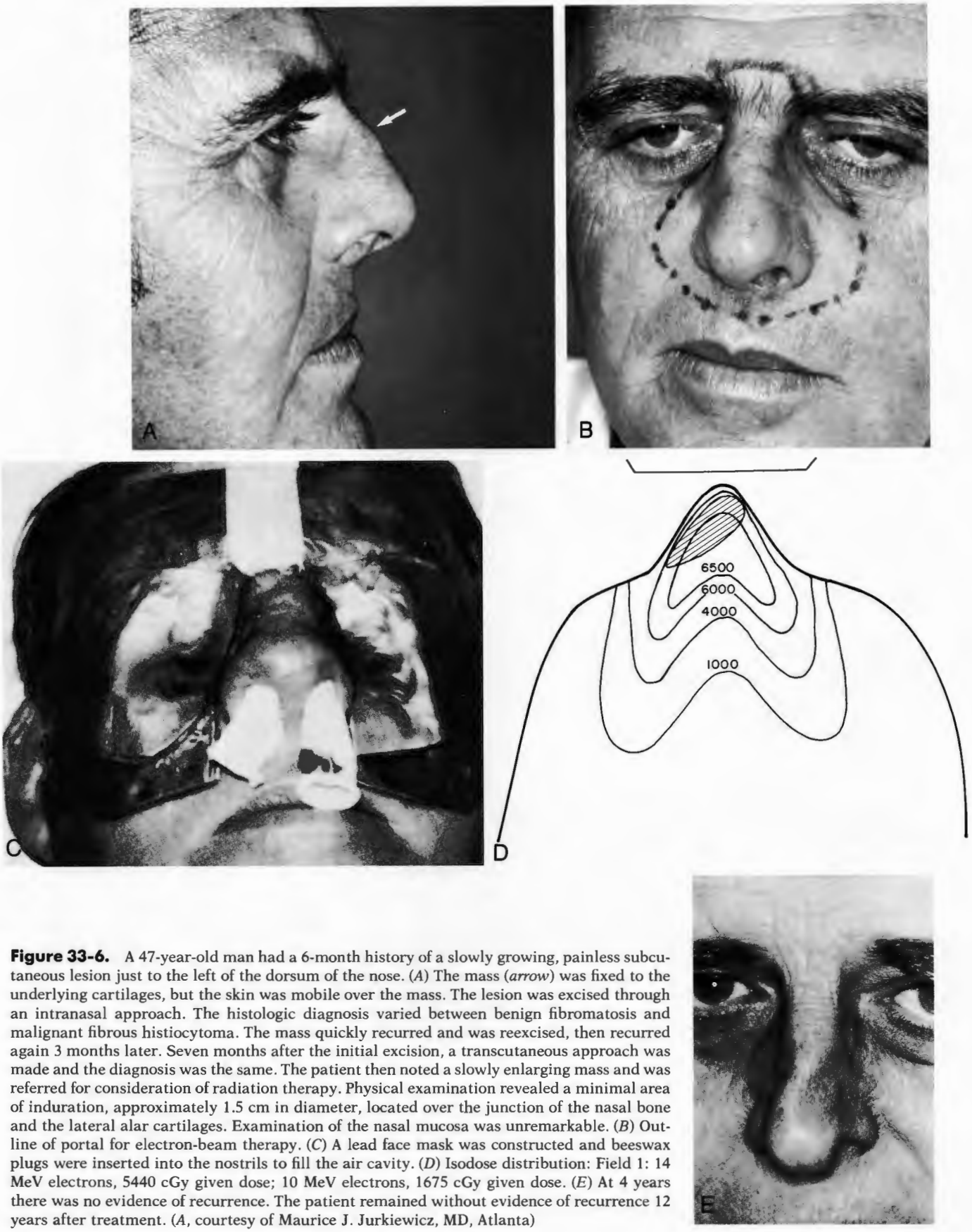

Figure 33-6. A 47-year-old man had a 6-month history of a slowly growing, painless subcutaneous lesion just to the left of the dorsum of the nose. (*A*) The mass (*arrow*) was fixed to the underlying cartilages, but the skin was mobile over the mass. The lesion was excised through an intranasal approach. The histologic diagnosis varied between benign fibromatosis and malignant fibrous histiocytoma. The mass quickly recurred and was reexcised, then recurred again 3 months later. Seven months after the initial excision, a transcutaneous approach was made and the diagnosis was the same. The patient then noted a slowly enlarging mass and was referred for consideration of radiation therapy. Physical examination revealed a minimal area of induration, approximately 1.5 cm in diameter, located over the junction of the nasal bone and the lateral alar cartilages. Examination of the nasal mucosa was unremarkable. (*B*) Outline of portal for electron-beam therapy. (*C*) A lead face mask was constructed and beeswax plugs were inserted into the nostrils to fill the air cavity. (*D*) Isodose distribution: Field 1: 14 MeV electrons, 5440 cGy given dose; 10 MeV electrons, 1675 cGy given dose. (*E*) At 4 years there was no evidence of recurrence. The patient remained without evidence of recurrence 12 years after treatment. (*A*, courtesy of Maurice J. Jurkiewicz, MD, Atlanta)

Figure 33-7. (*A*) A 69-year-old Samoan woman had a 1-year history of a slowly enlarging mass on the right side of her neck. Roentgenogram showed erosion on the medial surface of the scapula due to pressure. Biopsy revealed aggressive fibromatosis. The lesion was considered unresectable, and 5500 cGy was delivered to the mass with cobalt-60. (*B*) Slow resolution of the mass occurred, with complete resolution 2 years after treatment. (Hill DR, Newman H, Phillips TL. Radiation therapy of desmoid tumors. Am J Roentgenol Radium Ther Nucl Med 1973;117:85, 87)

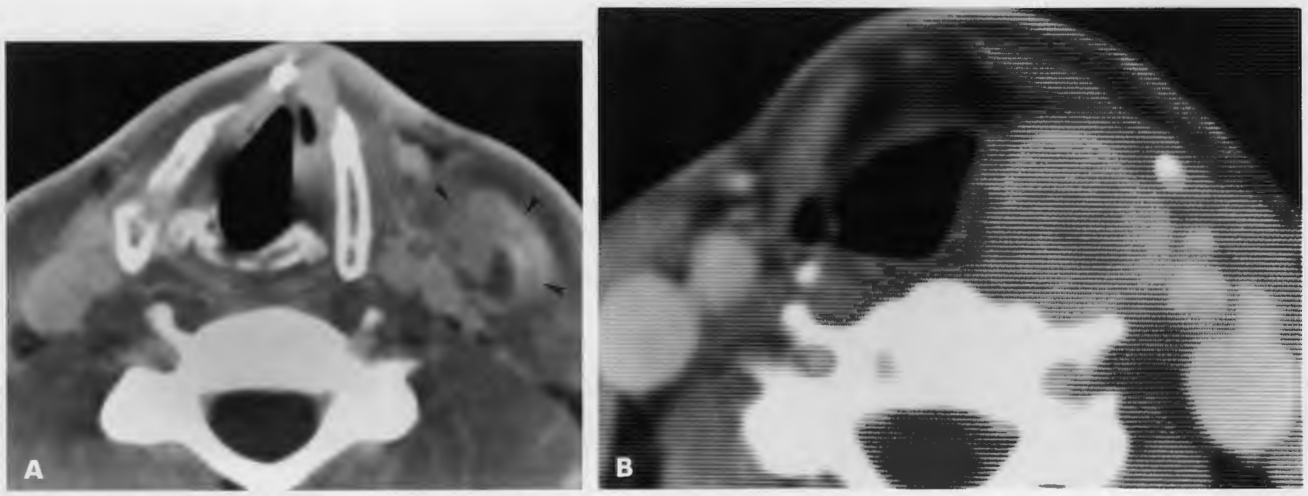

Figure 33-8. Two patients who had lesions with a predominantly fibrous makeup. (*A*) A 35-year-old man presented with a slightly painful, tender neck mass. Axial contrast-enhanced CT revealed an enhancing mass (*arrowheads*) within the sternocleidomastoid muscle, eventually diagnosed as fibrosing myositis. (*B*) A 53-year-old man complaining of dysphagia had a submucosal mass in the pyriform sinus region. Axial contrast-enhanced CT shows a well-defined, enhancing mass appearing much like the one see in *A*. Biopsy revealed aggressive fibromatosis. *Comment*: Neither CT nor MRI is capable of differentiating low-grade (or benign) from high-grade fibrous lesions or, for that matter, from other types of masses that can arise at these sites. For instance, the lesion in *B* could easily have been a schwannoma of the sympathetic chain.

Dermatofibrosarcoma Protuberans

Dermatofibrosarcoma protuberans is a low-grade malignancy arising from the dermis. It may occur at any age, but it most often occurs in the middle decades of life. It begins as a small, firm, either red or bluish subcutaneous nodule. There may be a history of a small tumor present for many years, and then a sudden growth occurs that may be painful. The lesion can occur anywhere on the body; about 15% occur in the head and neck area. It has the appearance of a low-grade sarcoma and is often misdiagnosed as low-grade fibrosarcoma. Metastases are uncommon but have been reported in a few cases.[3]

The usual treatment is wide local excision. Local recurrence may develop if margins are inadequate. Initially, the lesion is usually a solitary mass, but multiple nodules may develop as it enlarges or recurs after inadequate surgery. Barnes and coworkers reviewed the literature and reported 17 cases occurring in the head and neck. Of 15 patients available for follow-up, 8 developed local recurrence after surgery.[3] This is somewhat higher than expected and probably reflects the difficulty in obtaining wide margins in the head and neck. Marks and associates reported a series of 10 patients treated with irradiation either for gross disease or in conjunction with surgery, with excellent results (only one local failure).[58] Doses similar to those used in sarcomas are recommended.

Metastasizing Sarcomas

Most soft tissue sarcomas of the head and neck present in the masticator and parapharyngeal spaces (infratemporal fossa) or neck, but they may occur anywhere. The prognosis and response of the tumor to treatment are dependent more on the grade, size, and location of the lesion than the histologic label, but there are exceptions to this general statement. The following tumors have some unique features that require a brief discussion (see also Chap. 32).

Hemangiosarcoma, also called angiosarcoma, may arise from the endothelial cells of almost any organ, including the skin; the head and neck region is the most common site.

The scalp is the predominant area of involvement, with the soft tissues of the face also being a common site. The tumor is usually blue or purple with peripheral zones of erythema and satellitosis. Hemorrhage and bleeding are common. The tumor tends to infiltrate deeply into the adjacent soft tissues for long distances, often surprising the surgeon at the time of the operation. It will invade bone and cartilage, but, interestingly enough, it tends to grow around skin adnexa and leave them intact.[5]

There is a male-to-female preponderance of 4 : 1. The tumor is most common in the older age-groups, but it has been reported even in the pediatric age-group.[32]

According to Batsakis and Rice, there are at least two histologic grades of angiosarcoma: low grade and high grade (undifferentiated).[5] The angiosarcomas of the scalp are most likely to be high-grade lesions and have a poor prognosis.

The treatment depends on the extent of local disease, as well as on the presence of metastatic disease at the time of diagnosis. Metastases to the cervical lymph nodes and lungs are manifested in about one third of the patients.[5] The treatment has been primarily surgery, although local recurrences are common, and after one or more failures, patients usually develop metastases. Rosai and coworkers advise surgical excision only for lesions that are solitary and well circumscribed.[75] They recommend that the others be treated primarily by radiation. Radiation therapy has also been reported by Spittle to be effective.[86]

Since the most common mistake made in treating these patients is to underestimate the volume of tissue at risk, the entire scalp, as a minimum, should be considered at risk. Consideration should also be given to treating both sides of the neck electively as well. Doses of 5000 cGy should be given to the areas treated electively, and at least 6500 to 7000 cGy should be given to the grossly involved regions at 180 to 200 cGy per day. Multiple electron fields may be needed, at least for the boost doses.

Occasionally, a rapidly dividing tumor may be encountered for which radiation treatment with one fraction per day may not be adequate. We have treated two such patients with two or three fractions per day with local control of disease to date. One had a large primary tumor of the tongue and the other had a primary tumor of the scalp.

The prognosis in head and neck angiosarcomas is poor. One half of the patients die within 5 years of diagnosis, and another one fourth of the patients are still living at 5 years with persistent or recurrent tumors. Patients with scalp lesions do even worse.[63] Lesions in the nose, ear, or lip have an earlier clinical presentation and therefore a potentially better chance of cure, but these are much rarer.

Hemangiosarcoma has also been reported by Dahlin to be primary in bone, although only one of his reported cases occurred in the head and neck region (in the skull).[23] The prognosis in primary hemangiosarcoma of bone is poor.

Malignant fibrous histiocytoma arises from tissue histiocytes and, until the 1970s, was an uncommon diagnosis. Now it is the most common histologic subtype of soft tissue sarcoma in most institutions. These tumors tend to invade along fascial planes, with well-defined margins and bulky masses that appear encapsulated but are not. They generally occur in adults older than age 40. The malignant lesions primarily spread to the lung.[4]

Liposarcoma is a tumor that most often arises in late adulthood. Occurrences in the head and neck are usually seen in the deep structures of the neck (Fig. 33-9). It is possibly the most radiosensitive of the soft tissue sarcomas.

Leiomyosarcoma and rhabdomyosarcoma may at times be difficult to distinguish histologically, although rhabdomyosarcoma is more common. Most rhabdomyosarcomas in adulthood are of the pleomorphic type, although the embryonal type does occur and an occasional alveolar variant has been noted (see Figs. 32-1 through 32-4 in Chap. 32). They are usually high-grade lesions and have a high rate of metastatic disease, with perhaps the poorest prognosis of any of the adult head and neck sarcomas with the exception of angiosarcomas.

Neurosarcoma presenting in the head and neck is primarily malignant schwannoma, which often occurs in early adulthood. It is essentially an orderly fibrosarcoma of nerve sheath origin that presents as a slowly expanding, encapsulated tumor. It is associated with neurofibromatosis of von Recklinghausen in a large number of

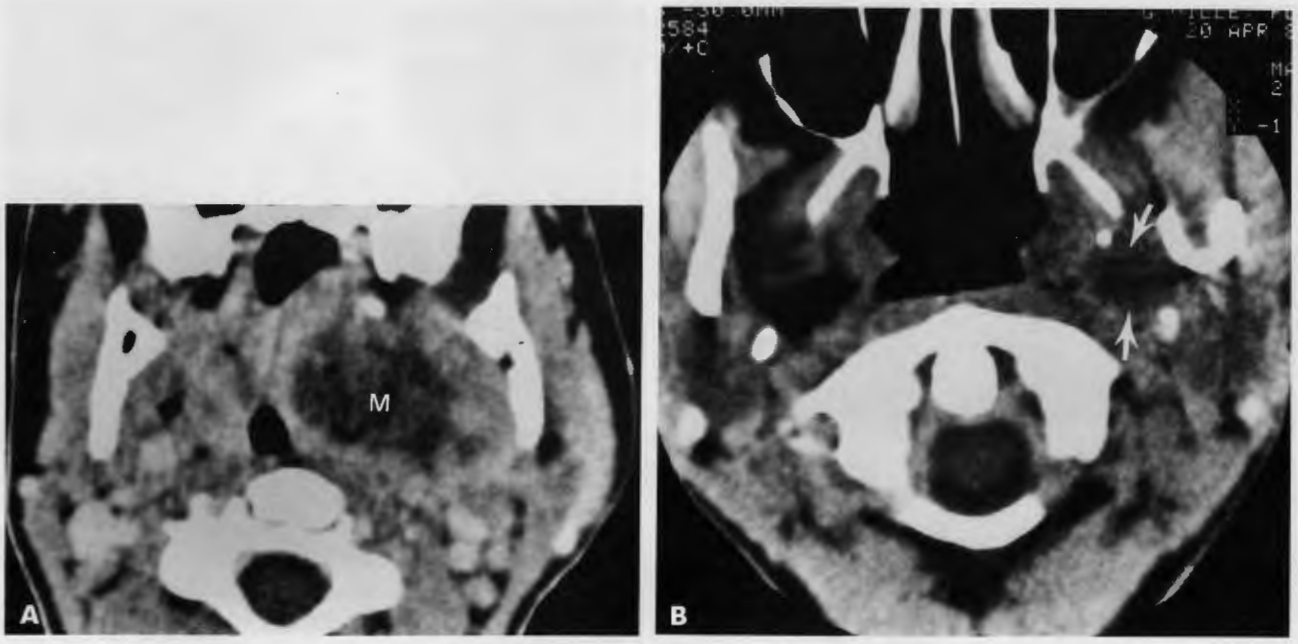

Figure 33-9. Two patients with parapharyngeal space sarcomas. (*A*) A 45-year-old woman had a submucosal mass in the oropharynx. Axial contrast-enhanced CT at the nasopharyngeal-oropharyngeal junction shows a low-attenuation mass (M) centered in the prestyloid parapharyngeal space. The attenuation within the mass is equivalent to that of fluid (compare with fluid in spinal subarachnoid space) so that the appearance is nonspecific. Biopsy revealed liposarcoma. (*B*) A 30-year-old woman had a 2-year history of burning in the left lateral tongue and intermittent pain while eating. CT without contrast enhancement shows tumor present in the left parapharyngeal space (*arrows*); the body of the mandible is minimally involved by tumor. Biopsy revealed hemangiopericytoma. The patient was treated with a partial resection and postoperative irradiation to 6500 cGy. She was without evidence of disease at 11 years.

patients. Most neurosarcomas occur in the infratemporal fossa and neck, but they also occur in the orbit, tongue, lip, and paranasal sinuses (Fig. 33-10).

A few undifferentiated sarcomas cannot be subclassified.

The work-up of patients with soft tissue sarcoma is directed at both local and metastatic disease. The primary site is evaluated with contrast-enhanced CT and MRI. Angiography is added according to the individual situation. The most common site of metastatic disease is the lungs; a CT of the chest is done if routine chest films are negative. Bone scans are done mainly to look for metastases. Bone invasion at the primary site is evaluated by high-resolution CT; it is important to exclude such bone involvement since this may influence the decision regarding resectability of the lesion.[27]

Although staging systems for soft tissue sarcomas have been developed, they are probably less useful in the head and neck than for primary lesions of the extremities.[80] In general, the prognosis depends on the grade, size, and resectability of the lesion (Table 33-1).[26] Soft tissue sarcomas of the head and neck region are not as well suited for radical resection as the lesions of the extremities. Because of this, to obtain local control, it is often necessary to add radiation therapy. For soft tissue sarcomas of the head and neck treated with a combina-

TABLE 33-1. Local Control of Soft Tissue Sarcomas According to Surgical Margins (No Adjuvant Treatment)

Margins	Low Grade	High Grade
Intralesional (piecemeal debulking or curettage)	10%	0%
Marginal (shell out through pseudocapsule or reactive zone of tumor)	30%	10%
Wide (intracompartmental *en bloc* with cuff of normal tissue)	90%	60%
Radical (*en bloc* resection of entire anatomic compartment)	100%	85%

(Adapted from Enneking WF. Musculoskeletal tumor surgery, vol 1. New York, Churchill Livingstone, 1983:99)

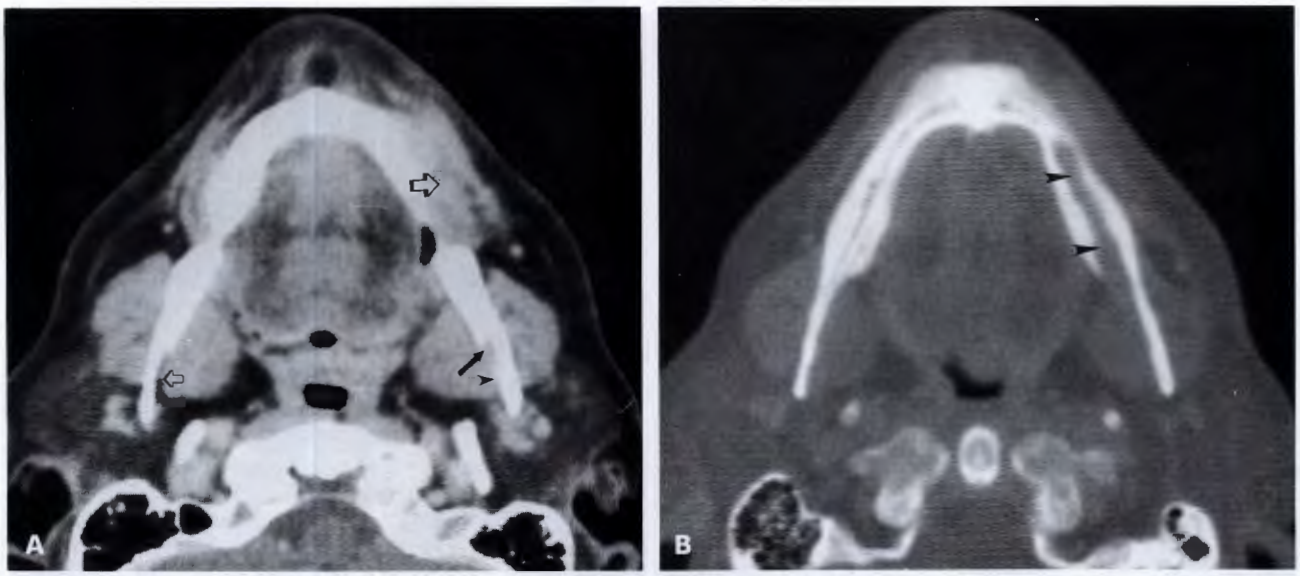

Figure 33-10. A 35-year-old woman with a neurogenic sarcoma involving the gingivobuccal sulcus and spreading along the inferior alveolar nerve. (*A*) Axial contrast-enhanced CT shows a mass in the gingivobuccal sulcus (*large open arrow*), widening of the mandibular foramen (*arrow*), and obliteration of the fat plane (*arrowhead*) between the medial pterygoid muscle and mandible; compare findings with normal side (*small open arrow*). (*B*) Axial CT about 1 cm inferior to that in *A* and photographed for bone detail shows widening of the inferior alveolar canal (*arrowheads*) due to perineural growth of tumor.

tion of surgery and postoperative radiation therapy at M. D. Anderson Hospital, Lindberg and associates reported that 12 of 19 patients were without evidence of disease at 5 years.[54] The local control rate was 84% in these patients. These researchers recommended postoperative radiation therapy with 6000 cGy tumor dose over 6 weeks for low-grade lesions and 6500 cGy tumor dose over 6½ weeks for intermediate and high-grade lesions, with a reduction in field size at 5000 cGy. The dose is higher with positive margins or gross residual disease. It is difficult to make specific recommendations regarding the volume of tissue to be treated, but it should be generous, taking into account the tissues contaminated at surgery and the extent of the hematoma. For high-grade lesions, consideration should be given to treating the regional lymphatics to 5000 cGy in 5 weeks.[33]

Preoperative irradiation should be considered in situations in which the lesion is borderline for resection. Our experience with large lesions of the trunk and extremities shows that large tumors will regress with 5000 cGy given preoperatively.[12] A reactive fibrous rim often develops, which may aid in dissection. Good local control, primarily in the trunk and extremities, has been reported with preoperative radiation therapy.[2,12,90]

The role of chemotherapy in soft tissue sarcomas is still unsettled. There is no doubt that various regimens will produce a measurable response in about 50% of patients, but few of these are complete responses.[91] Trials using adjuvant chemotherapy have been even more disappointing, with only one series showing increased survival. Rosenberg and coworkers reported an improved disease-free survival and absolute survival using adjuvant cyclophosphamide, doxorubicin (Adriamycin), and methotrexate in extremity lesions.[77,78] Longer follow-up revealed no difference in absolute survival but a persistent significant difference in disease-free survival (75% versus 54%).[16,17(p 1380)] Unfortunately, although it was randomized, this trial did not stratify for tumor size and is therefore of questionable significance. In addition, numerous studies have been unable to verify these results or show any significant advantage to multiagent chemotherapy.[25] Because of the extremely high rate of distant metastasis with large high-grade lesions, further trials are warranted.[2,12,90]

Kaposi's Sarcoma

First described by Moricz Kaposi as "idiopathic, multiple, pigmented sarcomas of the skin," this entity is now divided into four types: African, renal transplant–associated, classic, and epidemic (acquired immunodeficiency syndrome [AIDS]–associated).[17(p 1345)] Histologically, the lesions of the four types are similar, showing interlacing bands of spindle cells with vascular structure. These vascular structures can be composed of cleftlike spaces with extravasated erythrocytes and lymphatics and blood vessels extending to the periphery of the lesion.[39(p 1959)] This accounts for the red to purple to brownish macules, nodules, or papules seen at presentation.

Because of the increasing number of patients with AIDS, there are more patients than ever being seen with AIDS-associated Kaposi's sarcoma. The incidence is about one of three in AIDS patients.[22] AIDS-associated Kaposi's sarcoma is much more common in homosexuals than heterosexuals.[17(p 1345),38,39,45,93] The male-to-female ratio is 20 : 1. In addition, because in homosexuals there is sometimes a clustering of lesions in the oropharynx or anal area, a possible direct, sexually transmissible agent has been suggested.[38] Although an association with

cytomegalovirus has been reported, the exact role of this or other infectious agents is uncertain.[81,93]

Because nonepidemic Kaposi's sarcoma uncommonly involves the head and neck and is rarely seen in mucosal sites, it will not be further discussed.

Epidemic (AIDS-associated Kaposi's sarcoma) lesions frequently occur in the skin of the head and neck and in mucosal sites, particularly the hard palate and the tip of the nose (Fig. 33-11).[9,29] Because of the natural history of AIDS, the treatment, prognosis, and clinical course of these patients vary. The response to treatment is difficult to monitor because of the progressive and frequently rapidly fatal outcome of the basic disease itself.[64] In addition, because there is some evidence that Kaposi's sarcoma lesions may spontaneously remit if the immune status is restored or improves, the results of treatment of Kaposi's sarcoma lesions in AIDS may be related to the immune status of the patient.[13,44,71]

According to Ficarra and coworkers, "the majority of patients with oral Kaposi's sarcoma do not require treatment because they are without symptoms."[29] With appropriate treatment of concomitant infection and improvement in oral hygiene, many of the oral lesions will become less painful and therefore will not require treatment (Quivey JM, personal communication, 1990).[29] Cosmetically unacceptable, painful, bleeding, or bulky lesions interfering with function are most commonly referred for treatment with irradiation. In addition, lesions about the eyes and eyebrows should be considered for treatment because severe edema may occur, causing blindness due to closure of the eyelids.[38]

Treatment Recommendations

Superficial skin lesions that are small should be treated with orthovoltage x-rays or electrons. Larger or deep lesions are usually treated with high-energy photons. Treatment volumes should be kept as small as possible for all areas of the head and neck.

Figure 33-11. Typical appearance of epidemic (AIDS-associated) Kaposi's sarcoma of the hard palate. Note the cluster of dark (blue), nodular lesions.

Lesions of the oral cavity, pharynx, and larynx are usually treated with parallel opposed lateral photon fields. The draining lymphatics are usually not treated. Doses and fractionation schedules vary, with schedules ranging from 650 cGy in a single fraction to 3500 cGy in 10 fractions.[21,48,66,87]

At the University of California at San Francisco, conjunctival lesions are treated with a 6-MeV electron field. The eye is open, and an external lens block is placed by the physician.[9] Although it has been advised that lesions of the eye and mucosal sites should probably not be treated with the large single-fraction method,[29,41] this policy is now being questioned. Berson and coworkers updated the series reported from the University of California at San Francisco and concluded that there does not appear to be a significant difference in the duration of control with various treatment regimens and that there is a lower incidence of severe reactions with use of 800 cGy in one fraction. They have therefore begun offering selected patients a single irradiation fraction of 800 cGy for lesions not only of the skin but also of mucosal sites.[9] Whether this will be as effective and safe as fractionated schemes requires further verification.

Results of Treatment

When evaluating response, it should be noted that these lesions may take 3 to 4 months to resolve and may leave a residual lesion.[9,15,22] Berson and associates defined response as "complete flattening of a lesion (usually there is some residual pigmentation) or decrease in the dimensions of the lesion to at least 50% of the pretreatment size with decrease in pigmentation." In addition, there should be some resolution of the symptoms (such as pain or edema) for which the patient was being treated. They also noted that most lesions treated for cosmesis "decreased in size, flattened, and underwent a decrease in pigmentation sufficient to allow adequate masking with make-up" (Fig. 33-12).[9]

The overall response rate in the series of 45 patients with lesions of the oral cavity, pharynx, and larynx was 91%. Unfortunately, however, in the entire series of 187 patients, the median survival was only 6 months (range, 0 to 61 months).[9] Other series have reported similar results and overall survival.[81,87]

Toxicity

Toxicity related to small-volume irradiation of skin surfaces is usually negligible.[22] Severe mucositis has been reported with irradiation of the mucosal surfaces, particularly with fractionated irradiation at a dose per fraction in the range of 300 to 400 cGy. At the University of California at San Francisco, decreasing the dose per fraction from 200 to 180 cGy reduced mucositis somewhat, and a further decrease in the dose per fraction to 150 cGy and in total dose to 1500 cGy further reduced mucositis. Freedom from relapse at 3 months remained high (85% to 88%). Based on observations of a small number of patients, treatment with a single irradiation fraction (800 cGy) to mucosal sites has not resulted in increased severe toxicity.[9]

Chemotherapy

For small lesions of the skin or mucosal surfaces, intralesional vinblastine injections can be an effective

Figure 33-12. (*A*) Small epidemic (AIDS-associated) Kaposi's sarcoma of the lower eyelid before therapy. (*B*) One year after treatment with 2400 cGy in 16 fractions (250 kV), the lesion had flattened but had not resolved completely.

treatment.[29] Patients who have had opportunistic infections and have widespread disease that cannot be palliated with irradiation can be treated with systemic chemotherapy. This, however, can cause leukopenia, which can predispose to opportunistic infections. Although multiagent chemotherapy has been used, single agents are usually recommended. Weekly alternating vincristine and vinblastine as well as bleomycin, methotrexate, and low-dose doxorubicin (Adriamycin) have been used.[9,38,39]

In addition, interferon alfa-2a has been used in patients who do not have a history of opportunistic infection.[38,39,73] Severe mucositis, however, was reported in two patients who were being treated with interferon and mucosal head and neck irradiation.[72]

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LYMPHOMAS AND RELATED DISEASES PRESENTING IN THE HEAD AND NECK

NANCY PRICE MENDENHALL

Non-Hodgkin's lymphoma and Hodgkin's disease are the most common malignancies of the hematopoietic system observed in the head and neck region. Hodgkin's disease and non-Hodgkin's lymphoma differ markedly in behavior and response to therapy. Hodgkin's disease has well-established histologic criteria for diagnosis and behaves as a single disease entity with predictable patterns of spread, predictable responses to both radiotherapy and chemotherapy, and excellent cure rates in both early and advanced disease. Non-Hodgkin's lymphomas behave as a diverse group of diseases ranging from some of the most indolent to the most aggressive malignancies. Histologic classification of the non-Hodgkin's lymphomas has been notoriously difficult; likewise, response to therapy in this group of diseases has been difficult to predict. Newer techniques for classification of the non-Hodgkin's lymphomas such as immunologic phenotyping, nucleic acid analysis with flow cytometry, and molecular genetic studies may be of help in explaining the apparent diversity of this group of diseases in the future; some of these studies require fresh tissue.

The treatment of any lymphoma requires close cooperation among the surgeon, the pathologist, the radiation oncologist, and the medical oncologist or hematologist-oncologist. The most common serious error in the management of head and neck lymphomas originating in extranodal sites is the incorrect interpretation of the biopsy specimen. The physician must be alert to this possibility; correlate the history, physical examination, and age of the patient; and be properly informed on methods of fresh-tissue examination to avoid serious therapeutic errors.

EPIDEMIOLOGY AND ETIOLOGY

According to American Cancer Society estimates, lymphomas accounted for about 4% of cancer diagnoses and cancer deaths in the United States in 1993.[9] The ratio of the two largest classes of lymphomas, Hodgkin's disease and non-Hodgkin's lymphomas, is about 1 : 5.

Forty percent to 60% of non-Hodgkin's lymphomas present in extranodal sites, and one third to two thirds of extranodal lymphomas occur in the head and neck area.[109,143] Hodgkin's disease presents almost exclusively in lymph nodes and is first noted in the low neck nodes in about 70% of cases.

Although a causal relationship between viral infection and lymphoma has not been proved, evidence of prior viral infection has been associated with two groups of non-Hodgkin's lymphomas. DNA and nuclear antigens from Epstein-Barr virus can be detected in the lymphoma cells of 90% of children with African Burkitt's lymphoma, an aggressive non-Hodgkin's lymphoma arising from B lymphocytes.[76] A retrovirus, T-cell leukemia/lymphoma virus (HTLV-1), has also been identified in the cells of patients with an aggressive form of peripheral T-cell lymphoma.[111] There appears to be an increased incidence of non-Hodgkin's lymphoma in states of immune deficiency, including congenital disorders (ataxia telangiectasia or Wiskott-Aldrich syndrome), pharmacologic immunosuppression (for prevention of rejection after organ transplantation or control of autoimmune disorders), and acquired immunodeficiency syndrome (AIDS).[54]

ANATOMY

The anatomy of lymph nodes in the head and neck area is described in Chapter 6. Other sites of lymphoid tissue in the head and neck region include Waldeyer's ring (the nasopharyngeal, palatine, and lingual tonsils), salivary glands, lacrimal glands, thyroid, and dermal lymphoid infiltrates. There is little or no lymphoid tissue in the eyeball, middle ear, or true vocal cords.

PATHOLOGY

Hodgkin's Disease

The diagnosis of Hodgkin's disease is based on the presence of typical Reed-Sternberg cells in an appropriate inflammatory background composed mainly of lymphocytes, histiocytes, and an abundance of eosinophils. The Reed-Sternberg cell, although necessary for the diagnosis, is not pathognomonic since it may also be seen in other diseases such as mononucleosis, thymoma, lung and breast cancers, and mycosis fungoides.[66]

The histologic subclassification of Hodgkin's disease most commonly used is that described by Lukes and Butler.[81] It is based on the increasing predominance of Reed-Sternberg cells and the decreasing prominence of a normal-appearing inflammatory background and includes four subtypes: lymphocyte predominant (LP), nodular sclerosis (NS), mixed cellularity (MC), and lymphocyte depleted (LD).

Non-Hodgkin's Lymphoma

The group of solid malignancies collectively called the non-Hodgkin's lymphomas is composed of a spectrum of diseases with a wide range of clinical presentations and biologic behaviors, all arising from lymphocytic cells with varying degrees of differentiation. The subclassification of non-Hodgkin's lymphoma is complex and requires the consultation of an expert hematopathologist for clarification. One of the most popular and clinically useful classifications for non-Hodgkin's lymphoma, the Rappaport system, divides lymphomas on the basis of histologic pattern and cellular appearance (Table 34-1).[6,61,62,100,115,141] Nodular lymphomas have a more indolent natural course than the diffuse lymphomas, except diffuse well-differentiated lymphocytic lymphoma, which may have a course similar to chronic lymphocytic leukemia.

Newer subclassifications have been proposed, such as Lukes and Collins' classification, the Kiel classification, and Dorfman's classification.[30,71,72,82] None of the newer classifications, including the Working Formulation, has proven to be superior to the Rappaport classification in terms of clinical use.[34] The difficulty with histologic subclassification is compounded by the fact that the histologic pattern of lymphoma may vary within a given patient. Variation of cell type in discrete areas within a single biopsy site is called "composite lymphoma."[53,68] When the architectural pattern varies between nodular and diffuse areas with a constant cell type, the lymphomas are called "mixed" and the prognosis is intermediate between that of nodular and diffuse.[36] "Discordant lymphomas" are those with different histologic features at different sites.[39,90] Additionally, the histologic pattern may evolve during the course of the disease; "transformation" refers to when the histologic findings change from low grade to high grade.[1,2]

Immunologic Phenotyping

The origin of many non-Hodgkin's lymphomas has been determined with immunohistochemical techniques that identify surface membrane monoclonal immunoglobulins known to be associated with either B or T lymphocytes.[54] Unfortunately, immunologic phenotyping does not correlate well with either the histologic subclassification of non-Hodgkin's lymphomas or the clinical behavior of the tumors. Immunophenotyping can be useful in dealing with small tissue samples (eg, fine-needle aspiration or effusions) and for differentiating a malignant (monoclonal) disorder from a benign (polyclonal) process or from Hodgkin's disease (polyclonal).

Nucleic Acid Analysis

The amount of DNA in tumor cells, as well as the fraction of tumor cells that is synthesizing DNA (S fraction), can be determined through flow cytometry. Studies correlating flow cytometry results with histologic findings and prognosis in lymphomas have shown that patients with diploid tumors and tumors with a small proportion of cells synthesizing DNA have a better prognosis.[4,89,144,145]

TABLE 34-1. Relative Distribution of Non-Hodgkin's Lymphoma According to Rappaport Classification (720 Patients)

Type	Nodular	Diffuse
Lymphocytic well-differentiated	1%	4%
Lymphacytic poorly differentiated	18%	17%
Mixed	13%	6%
Histiocytic	6%	31%
Undifferentiated		4%
TOTAL	38%	62%

Data from Bloomfield and coworkers,[6] Johnson and coworkers,[61] Jones and coworkers,[62] and Veranesi and coworkers.[141]
(Million RR. The lymphomatous diseases. In: Fletcher GH, ed. Textbook of Radiotherapy, ed 3. Philadelphia, Lea & Febiger, 1980:622)

PATTERNS OF INVOLVEMENT AND SPREAD

Hodgkin's Disease

Hodgkin's disease presents in lymph nodes in about 98% of cases. When two to four sites are involved, the involved nodal groups are contiguous in about 90% of cases. This spread pattern is most consistent with a unifocal origin and dissemination through lymphatic pathways.

The most common lymph node groups involved with Hodgkin's disease are the lower cervical and supraclavicular lymph nodes. Upper neck node involvement is infrequent. When upper nodes are involved, the preauri-

cular nodes are at risk as well. Patients with supraclavicular lymphadenopathy or bilateral neck disease have a 30% to 40% incidence of disease below the diaphragm in either the spleen or nodes in the splenic hilum, porta hepatis, celiac axis, or paraaortic chains. About two thirds of patients with Hodgkin's disease have early stage (I and II) disease.

Involvement of extranodal sites such as Waldeyer's ring is uncommon in Hodgkin's disease, and a diagnosis of Hodgkin's disease originating in an extranodal site must be regarded with suspicion. Direct extension into extranodal tissue occurs when the tumor breaks through the nodal capsule and invades an adjacent structure. Extranodal extension in Hodgkin's disease most often occurs with bulky mediastinal adenopathy where tumor may invade the lung, pericardium, and pleura.

Non-Hodgkin's Lymphoma

In the M. D. Anderson experience, about 60% of patients with non-Hodgkin's lymphoma with early-stage disease with unfavorable histologic findings had extranodal presentations and about 60% of these extranodal presentations occurred in the head and neck.[143] The most common sites of presentation in the head and neck are the cervical lymph nodes and Waldeyer's ring. Lymphoma accounts for less than 10% of malignancies arising in the nasopharynx and nasal cavity,[119,129] 5% of those in the tonsil, 3% of those in the base of the tongue,[100] and 2% of those in the parotid.[44] Histologically, most extranodal lymphomas are diffuse and intermediate to high grade except for those arising in the orbit, the canine fossa, and the major and minor salivary glands where low-grade lesions are common.[58] The most common histologic subtype in extranodal lymphomas is diffuse large cell (diffuse histiocytic) lymphoma.

Although contiguous lymph node involvement and spread occurs, non-Hodgkin's lymphomas tend to be generalized at the time of presentation much more often than Hodgkin's disease. Histologic findings are important when predicting prognosis. There is widespread disease at presentation, often with bone marrow involvement, in 70% to 80% of patients with nodular lymphomas. For diffuse lymphomas, however, 30% to 40% of patients have localized, stage I and II disease. Non-Hodgkin's lymphoma is more often localized in extranodal rather than nodal presentations. There is an association between involvement of Waldeyer's ring and the gastrointestinal tract. About 15% of patients with Waldeyer's ring lymphoma will relapse in the gastrointestinal tract when treated with involved field radiotherapy and vice versa.[3,12,85,124] A relatively favorable prognosis has been associated with lymphomas arising in gut-associated lymphoid tissue such as Waldeyer's ring and the gastrointestinal tract.[48]

CLINICAL PICTURE

Hodgkin's Disease

Patients with Hodgkin's disease tend to be younger than those with non-Hodgkin's lymphomas. The median age at onset for Hodgkin's disease is 35 years. Unlike other malignancies, it has a bimodal pattern of incidence with a large peak between the ages of 15 and 30 years and a smaller peak at about 50 years of age. About half of all patients with Hodgkin's disease are between the ages of 15 and 30 at the time of diagnosis. Hodgkin's disease is rare in children younger than age 5 or in persons older than age 60. The male-to-female ratio is about 1.5 : 1 for all patients and about 9 : 1 in patients younger than 10 years of age. About 40% of patients with Hodgkin's disease report systemic (B) symptoms such as fever, night sweats, or weight loss. Since the vast majority of patients with Hodgkin's disease have cervical lymphadenopathy, it is important to distinguish enlarged neck nodes caused by infection from those caused by Hodgkin's disease. (See Chapter 15 for differential diagnosis of a neck mass.) Lymph nodes involved by Hodgkin's disease are usually mobile, plump, rubbery, and nontender. The lymph nodes may be discrete but are often matted together. The most commonly involved nodes are the lower internal jugular or supraclavicular lymph nodes. Inflammatory nodes are usually smaller, softer, flatter, and tender and involve both the internal jugular and spinal accessory chains. Lymph nodes involved in Hodgkin's disease may wax and wane over a period of weeks to months before slowly enlarging. A few patients have numerous, bilateral, pea-sized nodes. Even the most experienced oncologist cannot differentiate lymphoma, carcinoma, and inflammatory lymph nodes purely on physical examination, but the age of the patient and location and palpable characteristics of the nodes are important factors in making the clinical diagnosis.

Non-Hodgkin's Lymphomas

Non-Hodgkin's lymphomas may present in either the lymph nodes or extranodal sites. Involved nodes are similar on palpation to nodes involved with Hodgkin's disease. Rapidly progressive growth is more common in non-Hodgkin's lymphomas than in Hodgkin's disease. Although internal jugular lymph nodes are most often involved, the occipital, preauricular, parotid, submaxillary, and submental nodes are more commonly involved in non-Hodgkin's lymphoma than in Hodgkin's disease.

The presenting symptoms in non-Hodgkin's lymphomas depend on the primary site. Systemic symptoms are much less common in non-Hodgkin's lymphomas than in Hodgkin's disease, with only 10% to 15% of patients presenting with a fever, night sweats, or weight loss. Nodal presentations, as in Hodgkin's disease, are usually asymptomatic masses discovered by the patient. The symptoms of non-Hodgkin's lymphomas occurring in extranodal head and neck sites are similar to those of squamous cancers in the same sites. Patients with lymphoma of the palatine tonsil usually have a unilateral sore throat or obstructive symptoms (Fig. 34-1). Physical examination usually shows an enlarged tonsil with a reddish, smooth mucosal covering. The lesions are often large and occlude the oropharynx. Concomitant neck adenopathy occurs in about 80% of patients. These lesions are difficult to differentiate from a hypertrophic, reactive tonsil in a young patient, and frequently the patient is treated with prolonged courses of antibiotics or with incision for a suspected tonsillar abscess.

The patients with base of tongue lymphomas may have obstructive symptoms, sore throat, and occasionally dysphagia or a change in voice. Lesions in the base of the tongue or pharyngeal walls are often submucosal bulging, and soft on palpation.

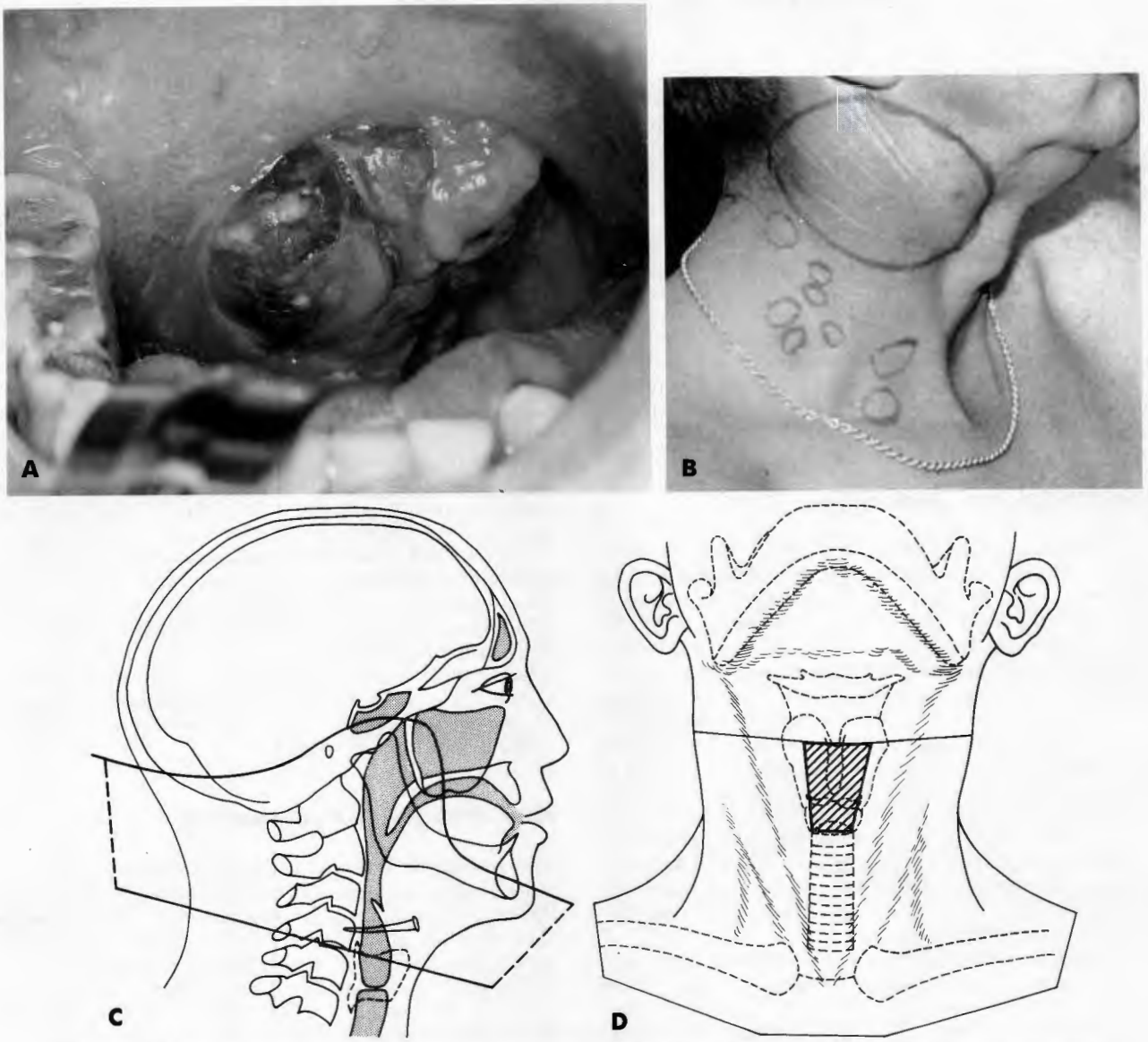

Figure 34-1. (*A*) Immunoblastic lymphoma involving the right tonsil in a 46-year-old man. Tonsillectomy was required because of rapid growth and airway obstruction. (*B*) Large lymph nodes outlined in ink on the patient's skin. This patient remains without evidence of disease 6 years after six courses of CHOP chemotherapy followed by 4000 cGy in 24 fractions to Waldeyer's ring and the neck. (*C*) Waldeyer's ring and neck fields are used for lymphomas of the nasopharynx, base of tongue, tonsil, and nodes. The superior border of the Waldeyer's ring field covers the nasopharynx as determined by bony landmarks and air shadows (*indicated by shading*) visible on the simulation film, the preauricular, postauricular, superior internal jugular, spinal accessory, and junctional nodes centrally, and the occipital nodes posteriorly. The anterior border extends caudad from the nasopharynx, covering the base of tongue and tonsillar fossae, then swings anteriorly, splitting the mandible to cover the submental nodes. The field flashes the skin both anteriorly and posteriorly to ensure adequate coverage of the submental and occipital nodes. The lower border is placed at the mid-thyroid notch and slanted to match the divergence of the low neck field as shown in *D*. Treatment is individualized in all cases. When occipital nodes are grossly involved, additional coverage of the posterior scalp is required. When parotid nodes are involved, additional anterior coverage is required. The Waldeyer's ring field is usually treated with cobalt-60. If the tumor is well lateralized and there is no contralateral adenopathy, the fields are weighted 3 : 2 in favor of the involved side so that the tumor bed receives 500 cGy to 750 cGy more than the contralateral neck. If the tumor is midline or extends to midline or if there is contralateral neck adenopathy, the fields are weighted 1 : 1. (*D*) Neck node field used in conjunction with Waldeyer's ring field. The upper border is hand-blocked to coincide precisely with the lower border of the Waldeyer's ring field. A narrow, tapered, midline larynx shield (*striped area*) extends from the thyroid notch to the lower border of the cricoid. The lateral margin is defined by the junction of the trapezius with the clavicle. The inferior border is usually 2 cm below the clavicle. (*E*) The majority of high-grade lymphomas greater than 2 cm in diameter are treated with three to six cycles of chemotherapy prior to radiation therapy. If pretherapy imaging studies are optimal, there is no nodal involvement, the primary tumor is small (less than 5 cm), and the response to chemotherapy is complete, the postchemotherapy field may be limited to cover only the primary site, as shown, and treated with cobalt-60 or 6-MV to 8-MV photons. (Shaded areas indicate air spaces.)

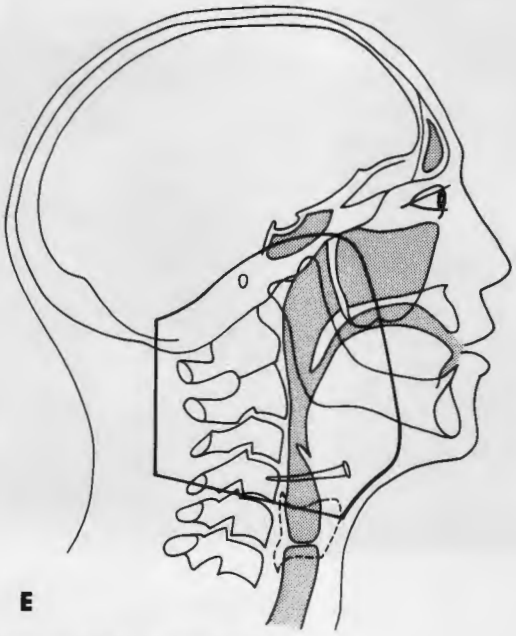

Figure 34-1. (*Continued*)

Patients with lymphomas in the nasopharynx may have intermittent hearing loss secondary to unilateral or bilateral eustachian tube obstruction or may have persistent epistaxis or nasal obstruction. Pain is rare. Many patients have neck node adenopathy. Cranial nerve palsy may occur but is uncommon.[84]

The salivary gland most commonly involved by lymphoma is the parotid, followed by the submandibular gland.[44] Patients with primary lymphomas of the parotid gland may have a painless mass or parotitis with massive enlargement of the parotid gland (Fig. 34-2). In about 15% of cases there is a preceding history of Sjögren's syndrome. The presentation of lymphomas in other salivary glands depends on the site; sites commonly involved include the palate (Fig. 34-3) and gingiva.[134]

Patients with lymphoma arising in the lid or conjunctiva complain of local irritation, itching, ptosis, and the sensation of a mass (Fig. 34-4). Proptosis and diplopia are the common presenting symptoms in patients with lymphomas arising within the orbit (Fig. 34-5). Pain is not a prominent symptom. Patients may also have blurred vision secondary to uveitis or hypopyon. Posterior uveitis is often associated with primary central nervous system lymphoma.[97,104] Anterior uveitis may occur but is less common.[45,130] Pseudotumor and benign lymphoid hyperplasia mimic orbital lymphoma. Distinguishing between benign lymphoid hyperplasia and low-grade lymphoma may be difficult for the pathologist. Certain histologic features are observed rarely but exclusively with lymphoma,[91] but neither monoclonality nor histologic findings accurately predicts for the likelihood of further evidence of lymphoma. Both histologically benign entities and lymphoma can occur as isolated presentations or in the setting of known disseminated lymphoma.[70] Polyclonal orbital lesions have occurred metachronously and synchronously with other evidence of lymphoma.[70,91] It is therefore important to evaluate the patient thoroughly before therapy and in posttherapy follow-up for progressive lymphoma, regardless of whether the initial orbital lesion is thought to be a benign lymphoid infiltrate or low-grade lymphoma.

Lacrimal gland lymphoma may present as epiphora or as a painless mass noticed for cosmetic reasons or

(*text continues on page 865*)

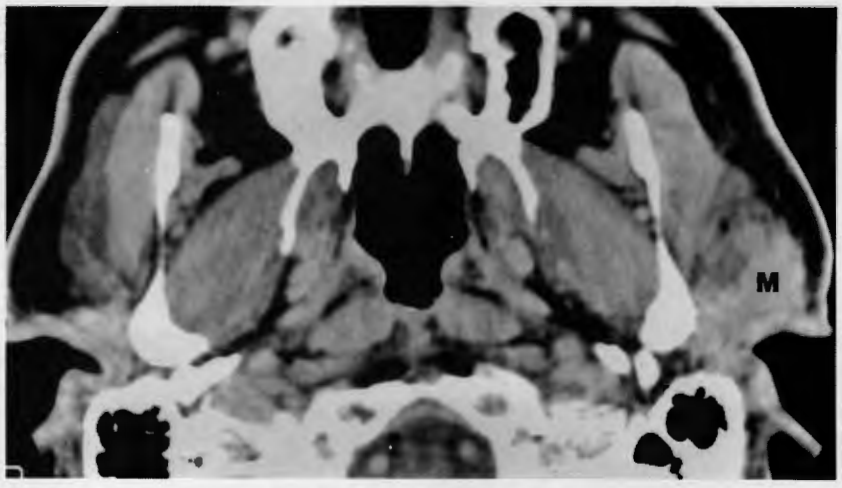

Figure 34-2. A 70-year-old man had a 2-month history of an asymptomatic enlarging lump in the left parotid area. There was no prior history of Sjögren's disease. CT demonstrated a mass (M) within the parotid that appeared infiltrative rather than encapsulated. There was no clinical or radiographic evidence of neck nodes. The superficial parotidectomy specimen showed a follicular mixed lymphoma diffusely infiltrating the parotid parenchyma that appeared to arise in an area of preexisting Sjögren's disease. This patient was treated with an ipsilateral parotid field with a combination of 20-MeV electrons and 6-MV photons and an ipsilateral low neck field. (The technique is described in Chapter 27.) The doses to the parotid field and neck field were 3500 cGy in 21 fractions and 3000 cGy in 18 fractions, respectively. The patient had no further evidence of disease 1 year after treatment.

Figure 34-3. This asymptomatic 59-year-old woman was noted by her dental hygienist to have a new hard palate mass (*arrowheads*) not present at her last visit 6 months before. There was no adenopathy. Clinically, minor salivary gland lymphomas are indistinguishable from other minor salivary gland tumors such as adenoid cystic carcinoma and from benign conditions such as lymphoid hyperplasia. The treatment field for this lesion was a Waldeyer's ring field, with modification of the anterior border to include the hard palate lesion with a 2-cm anterior margin, and a standard low neck field. The dose was 3500 cGy in 21 fractions to the hard palate lesion and 3000 cGy in 18 fractions to the clinically negative adjacent nodal and extranodal structures in Waldeyer's ring and neck fields. The tumor completely regressed during treatment, and the patient had no further evidence of disease 2 years after therapy.

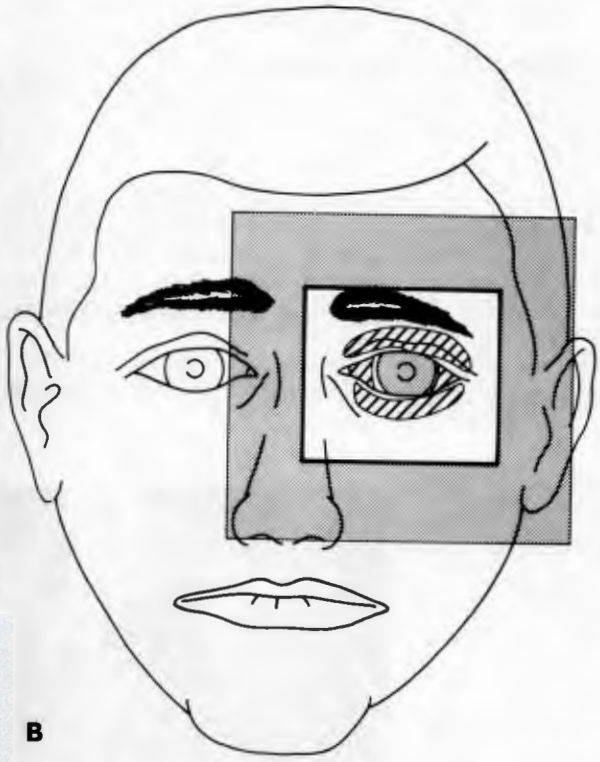

Figure 34-4. (*A*) Diffuse small cleaved-cell lymphoma (*arrow*) limited to the conjunctiva. (*B*) For lesions confined to the anterior orbital structures such as the conjunctiva or lid, an anterior field only is used. Orthovoltage x-ray therapy is preferable to electron-beam therapy because it produces less scattered irradiation to the cornea and lens beneath the corneal shield. With orthovoltage x-ray treatment, secondary blocking on the skin with a lead cutout shield (*shaded area*) is required. (Striped area indicates tumor.) (*C*) Actual treatment setup. The corneal shield (*arrow*) is applied after anesthetizing the eye with Ophthaine HCl drops. Strings attached to the corneal shield are secured with tape to prevent slippage of the shield during treatment. The lead mask used for secondary collimation of the field is molded to fit the patient's contour (see Chap. 25).

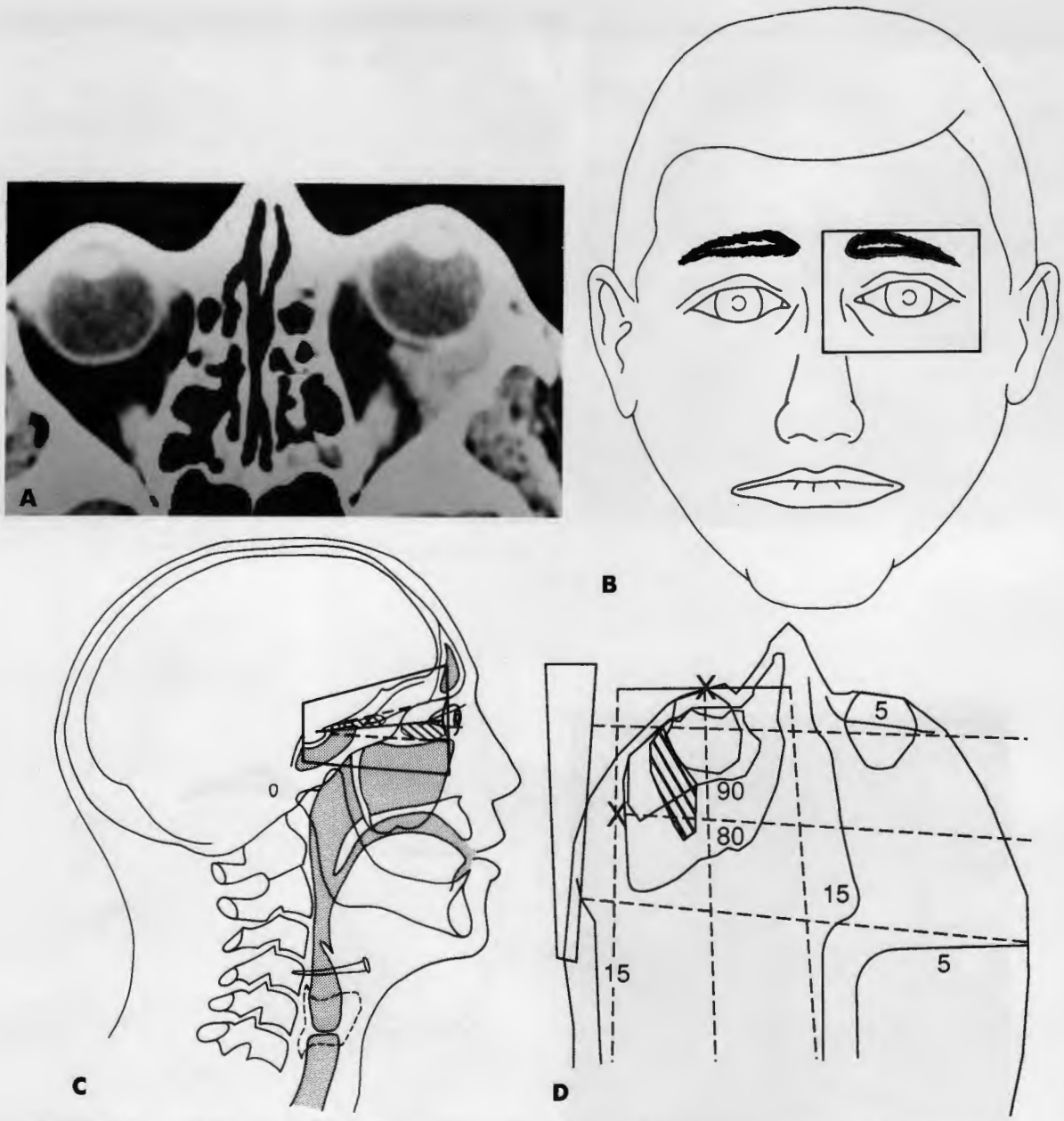

Figure 34-5. (*A*) CT scan of diffuse large-cell lymphoma in the left orbit posterior to the globe in an otherwise asymptomatic 71-year-old woman. There is tumor in the lateral orbit displacing the eye anteriorly. Intraorbital lesions are treated with anterior and lateral wedged fields. The apex of the orbit angles medially and superiorly; the patient's neck is extended so that the orbital apex is perpendicular to the anterior radiation beam. The appropriate amount of neck extension can be verified at simulation by setting the field delineators on the superior and inferior borders of the anterior field and then rotating the fluoroscopy unit 90° laterally to verify that the anterior clinoid (which is located just posterior to the apex of the orbit) is centered between the superior and inferior delineators. (*B*) Anterior field: The medial border of the anterior field is placed at midline to ensure coverage of the medial aspect of the orbital apex. The anterior field is treated with the eye open to perserve corneal sparing with the photon beam. If the patient has difficulty in keeping the eye open, a lid retractor may be used. (*C*) Lateral field: The anterior border of the lateral field is placed at the bony canthus; the lateral field is angled 5° posteriorly to avoid divergence into the contralateral lens. The lateral field is shaped with a block made of Lipowitz's metal to provide a 1.5- to 2-cm margin around the apex, which is indicated by the dotted line. If there is no anterior component to the tumor (posterior striped tumor volume only), 6- to 8-MV photons may be used. If the tumor extends anteriorly (anterior striped tumor volume), cobalt-60 is used. (Shaded areas indicate air spaces.) For benign disorders such as pseudotumor and Graves' disease without anterior orbital extension, a lateral field may be used alone. Doses commonly used are 1500 to 2000 cGy in 10 fractions for benign disorders, 1500 to 2500 cGy in 150- to 165-cGy fractions for low-grade lymphomas, 4500 cGy in 25 fractions for high-grade lymphomas treated with radiation therapy alone, and 4000 cGy in 22 fractions for high-grade lymphomas treated in conjunction with chemotherapy. (*D*) Dosimetry of the field arrangement at the central axis. (Striped areas indicates tumor.) The anterior field is open and weighted 1.0 while the lateral field is treated with a 45° wedge filter and weighted 0.5. The dose is specific to the 80% isodose line. If the specified dose is 4500 cGy, as in this case, the contralateral lens receives 280 cGy.

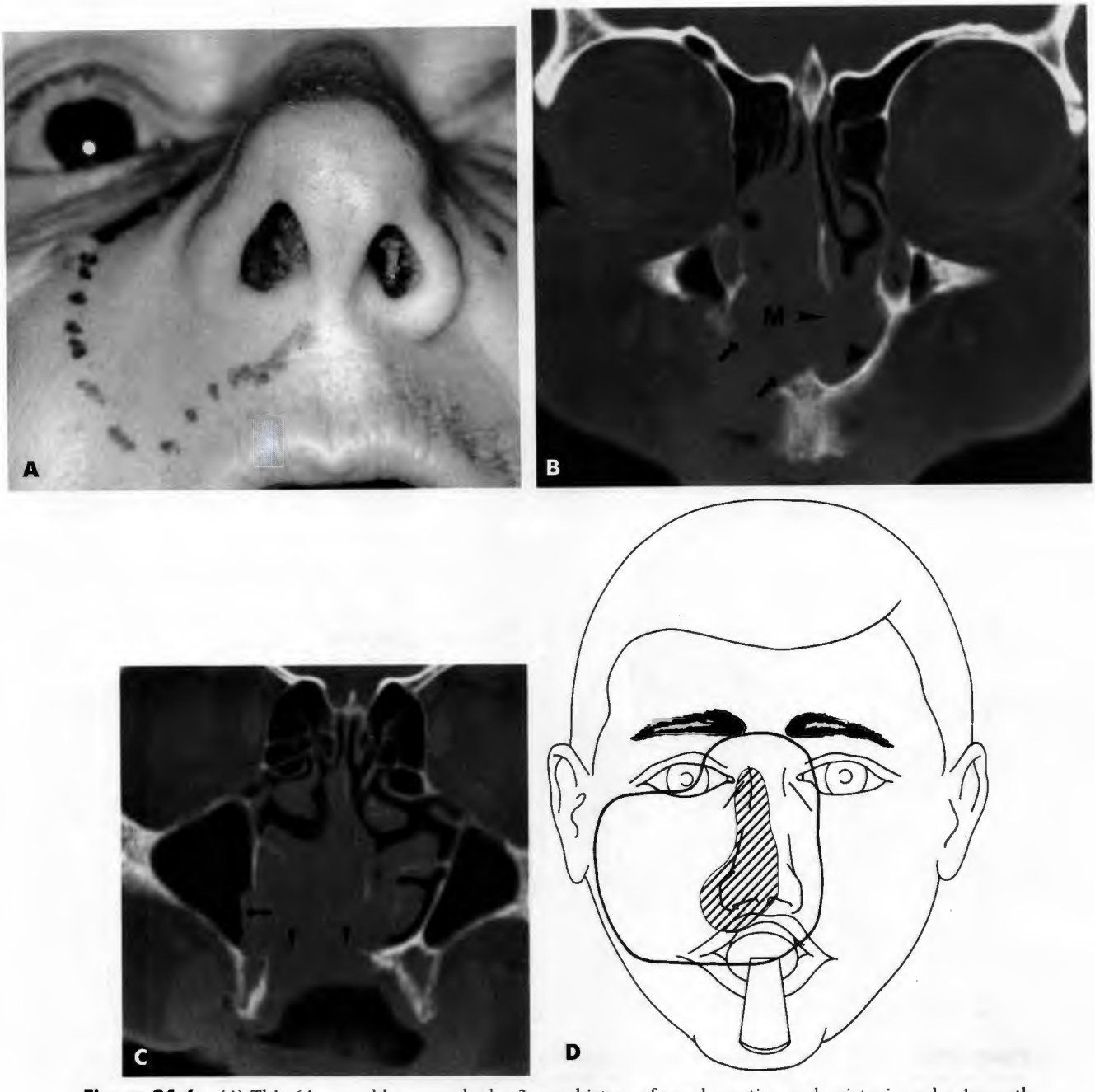

Figure 34-6. (*A*) This 64-year-old woman had a 3-year history of nasal crusting and epistaxis and a 1-month history of rapidly progressive right nasal obstruction. Physical examination demonstrated a red, fleshy lesion filling the right nasal vestibule and cavity. An associated mass was palpable in the premaxillary space (*dotted line*), and a 2-cm area of erythema was visible on the right hard palate. (*B*) Coronal CT through the orbit, anterior ethmoid sinus, and premaxilla demonstrated a mass (M) filling the right nasal cavity, destruction of the septum (*arrowhead*) with left nasal cavity extension, and destruction of the right premaxilla with an associated soft tissue mass (*arrows*). (*C*) Coronal CT through the posterior ethmoid, nasal cavity, and anterior oral cavity demonstrated minimal involvement of the right maxillary sinus (*arrowheads*) and destruction of the right side of the hard palate (*arrow*). Biopsy showed diffuse large cell (B cell) lymphoma. Following partial response to three courses of chemotherapy, 4000 cGy in 25 fractions was delivered to the original involved field using cobalt-60. After irradiation, an additional three cycles of chemotherapy were given. The patient had a local recurrence 2 months after completion of chemotherapy and obtained only brief remissions from further efforts with chemotherapy. (*D*) The anterior field includes the right and left nasal cavities, the right maxillary sinus, and the right hard palate. (Note that coverage of the maxillary sinus requires coverage of the medial inferior quadrant of the orbit.) A beeswax plug inserted in the right nasal vestibule ensures adequate dosage to the superficial, visible portion of the tumor. A tongue depressor displaces the oral tongue, floor of mouth, and lower lip inferiorly. (Striped area indicates tumor.) (*E*) The lateral field includes the maxillary sinus and posterior hard palate with a 1.5- to 2.0-cm margin. (Striped areas indicates tumor; shaded areas indicate air spaces.) (*F*) The isodose distribution achieved with this field arrangement. The anterior open field was weighted 1.00, the anterior 30-degree wedged field was weighted 0.33, the right lateral 30-degree wedged field was weighted 0.50, and the left lateral 30-degree wedged field was weighted 0.25. The dose was specified to the 80% isodose line. (Striped area indicates tumor.)

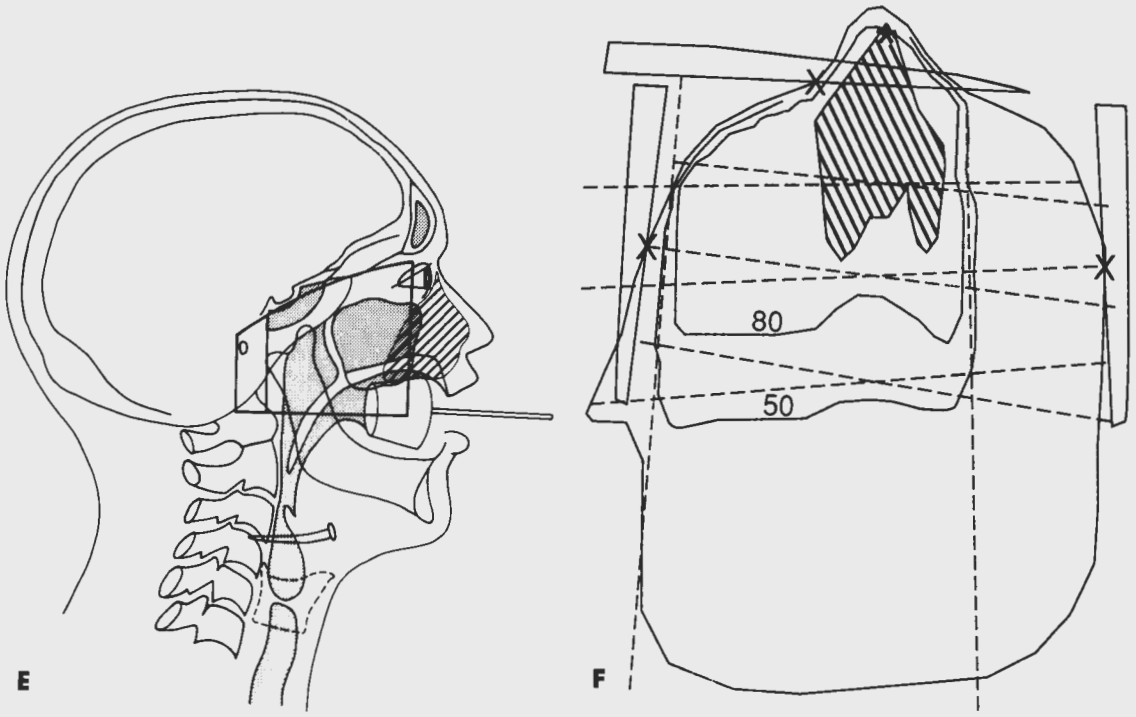

Figure 34-6. (*Continued*)

because of ill-fitting glasses. Other symptoms may develop when the disease spreads to adjacent sites such as the orbit, nasal cavity, and sinuses.

The maxillary sinus is the paranasal sinus most frequently involved by lymphoma. Maxillary sinus lymphomas may present as facial fullness, sinusitis symptomatology, or odontogenic pain.[33,37] Proptosis and epiphora indicate orbital and lacrimal gland extension.[84] Nasal obstruction and epistaxis indicate nasal cavity spread.

Initial symptoms of nasal cavity lymphoma include nasal obstruction with epistaxis (Fig. 34-6). Proptosis and facial fullness or pain indicate orbital and maxillary sinus invasion. Although the majority of nasal cavity lymphomas reported from the Orient are peripheral T-cell malignancies, in the United States and Europe most are B-cell lesions.[37,42] Clinically it is difficult to distinguish nasal cavity lymphoma from lethal midline granuloma, a clinical syndrome characterized by progressive ulceration and erosion of the nose and paranasal sinuses. Some cases of lethal midline granuloma are apparently caused by inflammatory and infectious agents, collagen vascular diseases, and unknown causes (Wegener's granulomatosis and idiopathic midline destructive disease). It is probable that most cases of lethal midline granuloma are in fact lymphoid malignancies, most likely T-cell lymphomas similar to those commonly seen in the Orient[116] or other high-grade lymphomas misdiagnosed because of associated inflammation (see also Chap. 22).

Rarely, malignant lymphoma can present as a mass in the canine fossa.[46] Lesions in this site usually involve the infraorbital nerve, often with resulting anesthesia in the area innervated by this nerve (Fig. 34-7). Although histologic evidence of a nodal origin may not be present, it is likely that lymphomas in this site arise from facial nodes in the canine fossa since perineural lymphomas are not common in other sites.

Non-Hodgkin's lymphomas of the thyroid gland may cause symptoms of airway obstruction. There is usually diffuse enlargement of one or both lobes on physical examination and often a history of concurrent Hashimoto's thyroiditis. Constant surveillance of patients with Hashimoto's thyroiditis by yearly physical examination and ultrasound will facilitate discovery of lymphoma at its earliest stages. A focal nodule in patients with Hashimoto's thyroiditis may be due to lymphoma, focal thyroiditis, adenoma, adenomatous hyperplasia, or carcinoma. Ultrasound-guided biopsy is an accurate means for differentiating these possibilities in nonpalpable nodules.

The jaw is a common site of presentation for the African type of Burkitt's lymphoma occurring in children, with 50% of cases arising in the maxilla or mandible. In the United States, this is rare but carries a prognosis similar to that of other primary bone lymphomas.[31]

Non-Hodgkin's lymphoma in the head and neck is also found in the larynx,[102] temporal fossa, and skin. Temporal fossa lesions may arise in the temporal bone[105] and present as lateral facial swelling (Fig. 34-8).

Although the most common malignancy in patients with AIDS is Kaposi's sarcoma (see Chap. 33), there is also an increased risk of diffuse high-grade non-Hodgkin's lymphoma. In a study of oral findings in homosexual men, 120 patients with AIDS (80%) had Kaposi's sarcoma; 44% of those had oral lesions.[127] Also, in the same study, 2% of patients with AIDS had oral lymphomas and 1% had oral squamous cell carcinomas.[127] The distribution of sites of involvement for lymphomas in patients with AIDS differs from those in patients without AIDS.[148] There is a marked increase in the frequency of brain, bone marrow, oral cavity, and rectal involvement. The oral cavity lymphomas observed in patients with AIDS often involve the hard palate and gingiva and

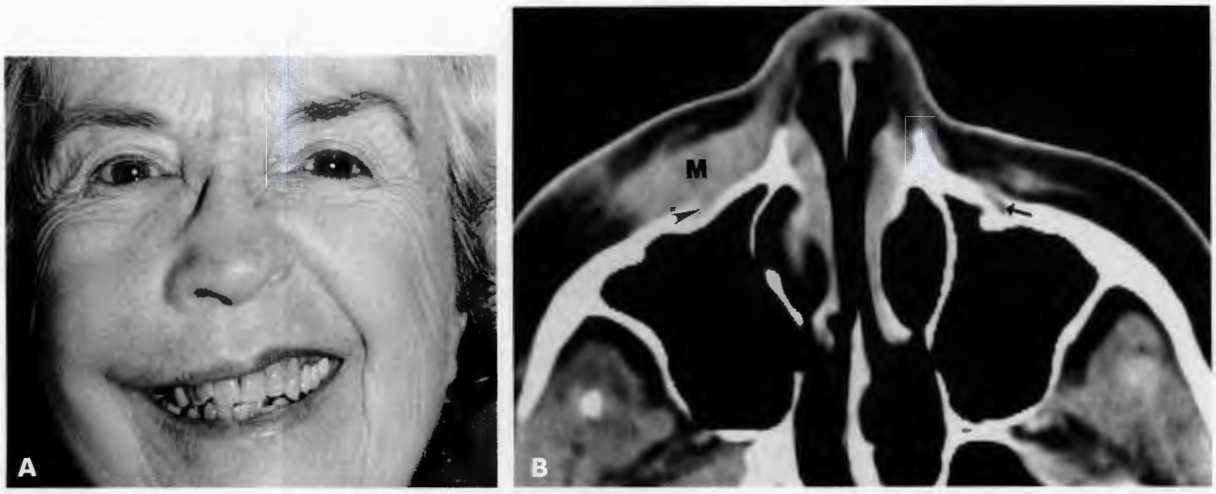

Figure 34-7. (*A*) This asymptomatic 75-year-old woman had a 3-month history of fullness in the right face. Note the mass in the right cheek and loss of the right nasolabial fold. Physical examination showed a 4 × 4-cm mass in the right canine fossa. (*B*) CT demonstrated a mass in the right canine fossa (M). Note the normal left infraorbital foramen (*arrow*) compared with the right infraorbital foramen, which is enlarged and eroded by tumor (*arrowhead*).

may be difficult to distinguish from other infectious and inflammatory processes that commonly occur in patients with AIDS.[49]

METHODS OF DIAGNOSIS AND STAGING

Biopsy Technique

In both Hodgkin's disease and non-Hodgkin's lymphomas, the initial biopsy technique is crucial for making the proper diagnosis. There are several general steps to follow in the diagnostic approach. The first step applies to head and neck cancers in general. In cases of cervical node presentation the clinician should first rule out the presence of a primary carcinoma or other malignancy by a thorough head and neck examination and proper biopsies (see Chap. 15). Even if the patient has already had a node biopsy from the neck confirming non-Hodgkin's lymphoma, a thorough head and neck examination should be undertaken to identify any extranodal sites of disease. If the patient presents without having undergone a biopsy, the first biopsy should be performed on the extranodal tissue, if possible. Occasionally, lymph node tissue will also be required to subclassify the lymphoma, or as an aid in differentiating a lymphoma from a poorly differentiated squamous carcinoma. If lymphoma is suspected, fresh tissue *must always be submitted for immunophenotyping and flow cytometry*, which can be a further aid in the diagnosis and subclassification of lymphoma. Whenever the size of the biopsy specimen allows, *tissue from the initial biopsy should be subdivided and a portion placed in electron microscopy fixative.* This is often helpful in defining the cell of origin for undifferentiated or anaplastic carcinomas that may be indistinguishable from lymphomas on histologic grounds alone.

If there is no extranodal tissue for the biopsy and the patient has undergone a thorough head and neck examination and work-up for an unknown primary lesion, then a lymph node biopsy should be done. The surgeon *should attempt to remove one of the largest nodes palpable.* Smaller nodes, while more easily removed, may not be representative, and this will necessitate repeat biopsies. The *lymph node should be removed by excisional biopsy* and, if possible, *with its capsule intact.* Even large lymph nodes can be only partially involved with lymphoma, and an incisional biopsy may not remove the tissue required for diagnosis. It is optimal to have the entire node for determining characteristic architectural changes in the node that aid in diagnosis and subclassification of the lymphoma. If the patient also has enlarged inguinal lymph nodes, biopsy of cervical nodes is usually preferred because of reactive or inflammatory changes frequently found in inguinal lymph nodes.

In general, the frozen-section technique cannot be used to make a diagnosis of Hodgkin's disease, but it can be used to guide the surgeon as to whether adequate tissue has been removed for the diagnosis.

Staging

The staging classification for both Hodgkin's disease and the non-Hodgkin's lymphomas in adults is the Ann Arbor staging classification:[16]

- I Involvement of a single lymph node region or of a single extralymphatic organ or site (IE)
- II Involvement of two or more lymph node regions on the same side of the diaphragm or localized involvement of an extranodal organ or site (IIE) and one or more lymph node regions on the same side of the diaphragm
- III Involvement of lymph node regions on both sides of the diaphragm, which may also be accompanied by localized involvement of an extranodal organ or site (IIIE), or spleen (IIIS), or both (IIISE)
- IV Diffuse or disseminated involvement of one or more distant extranodal organs with or without associated lymph node involvement

Systemic symptoms are denoted by the suffix letter B. The absence of systemic symptoms is denoted by the suffix letter A. Systemic, or B, symptoms include unexplained fever greater than 38°C (100.4°F), night sweats, and unexplained weight loss greater than 10% of the body weight over the past 6 months.

Figure 34-8. (*A*) This 40-year-old asymptomatic woman had rapid onset of swelling on the left side of her face. (*B*) Axial T1-weighted MRI demonstrated the anterior and posterior extent of the temporal fossa tumor (*arrowheads*). (*C*) Coronal T2-weighted MRI demonstrated the infratemporal fossa and intracranial extension. Involvement on both sides of the temporal bone raised the question of whether the primary site was actually bone rather than temporal fossa. Biopsy showed a diffuse large cell (B cell) lymphoma. Following a complete response to six courses of CHOP chemotherapy and a single dose of intrathecal methotrexate, the patient received 3000 cGy in 15 fractions to the entire brain followed by 2000 cGy in 10 fractions to the tumor bed through anterior and lateral fields. The patient had no evidence of disease 3 years after completion of therapy.

Initial Evaluation

Hodgkin's Disease

After a diagnosis of Hodgkin's disease has been rendered, a detailed history should be obtained with special attention to the presence of systemic symptoms. Physical examination should be done with emphasis on the lymph node regions, spleen, liver, and Waldeyer's ring. The laboratory evaluation includes a complete blood cell count, including platelet and differential counts; erythrocyte sedimentation rate; renal function evaluation; and liver function tests.

Routine radiologic studies should include posteroanterior and lateral chest roentgenography and computed tomography (CT) of the chest, abdomen, and pelvis. Most centers treating large numbers of patients with Hodgkin's disease continue to perform lymphangiography routinely. Both CT and lymphangiography are excellent when negative at predicting the absence of disease in the low paraaortic and pelvic nodes. When positive, neither is particularly reliable, but both may guide the surgeon at laparotomy. Lymphangiography can be additionally beneficial in treatment planning and posttherapy follow-up. None of the available radiographic methods (including CT,[17,87] ultrasound, and gallium scan) are reliable for detecting the presence of Hodgkin's disease in the spleen.

A bone marrow biopsy should be performed, especially in patients with clinical stage III disease or greater who have unexplained low blood cell counts or B symptoms.

A decision must be made in the course of the work-up of each patient with Hodgkin's disease as to whether to do a staging laparotomy, including abdominal exploration, splenectomy, liver biopsy, and multiple node biopsies. This decision hinges on the therapeutic policies of the physicians and varies from one institution to the next.

Non-Hodgkin's Lymphomas

A higher percentage of patients with non-Hodgkin's lymphomas will present with advanced-stage disease; therefore, staging of these patients requires a sequential

approach so that unnecessary tests can be avoided. A detailed history with reference to systemic symptoms is important, although only a small percentage of patients with non-Hodgkin's lymphoma have systemic symptoms. The physical examination should thoroughly evaluate all nodal regions, including epitrochlear, brachial, and popliteal nodes. A thorough head and neck examination should be done, with close attention to Waldeyer's ring. The routine laboratory tests are the same as in Hodgkin's disease. The radiographic tests are similar to those obtained in Hodgkin's disease with two exceptions. Patients with Waldeyer's ring involvement with equivocal abdominal CT or any gastrointestinal symptoms should have an upper gastrointestinal series and barium enema because of frequent gastrointestinal tract involvement. In non-Hodgkin's lymphomas, the lymphangiogram is less useful than CT of the abdomen and pelvis, not only because of frequent gastrointestinal involvement, but also because of the predilection in non-Hodgkin's lymphoma for involvement of mesenteric nodes, which are not imaged on lymphangiogram.

All patients with non-Hodgkin's lymphomas should have a bone marrow biopsy, preferably of both iliac crests. The majority of patients with nodular lymphomas have positive findings on bone marrow biopsy, placing them in a stage IV category.

Exploratory laparotomy is seldom indicated to make a therapeutic decision in the management of non-Hodgkin's lymphoma.

TREATMENT

Hodgkin's Disease

The curative treatment of Hodgkin's disease can consist of radiation therapy alone, chemotherapy alone, or a combination of both. Adults with early stages of Hodgkin's disease (stage I, stage II, and favorable stage IIIA) are usually treated with radiation therapy alone. Patients with intermediate stage disease (IIB, $IIIA_1$) may be treated with radiation therapy alone or combined modality therapy, often using only two or three courses of chemotherapy followed by irradiation. Even though relapse rates are higher after radiation therapy alone for intermediate stage disease, the ultimate survival rates are similar whether radiation therapy alone or combined modality therapy is used at the outset. Radiation therapy alone is the favored option at many institutions because it avoids the acute and late toxicities of chemotherapy for many patients.[75,88,113] Patients with $IIIA_2$ disease, extensive spleen involvement, or IIIB disease do poorly with radiation therapy alone and should receive combined modality therapy.[86,113,131] The combination chemotherapy regimens commonly employed are MOPP (mustargen [nitrogen mustard], vincristine [Oncovin], procarbazine, prednisone), ABVD (doxorubicin [Adriamycin], bleomycin, vinblastine, and dacarbazine [DTIC]), and alternating MOPP-ABVD regimens. The ABVD and alternating regimens appear to be at least as effective as MOPP but have not had the long follow-up experience of MOPP and carry different toxicity risks.[7,23,64,79,96,125,139,140,142] Although combination chemotherapy without radiation therapy has been used in intermediate[26] and advanced stage disease, relapses in the original sites of nodal involvement are common.[8,79] In most cases, combined modality treatment with both chemotherapy and radiation therapy will offer the patient with advanced disease the best chance of cure.[11]

When Hodgkin's disease is treated with radiation therapy, a dose of 3500 cGy at 150 to 170 cGy per fraction appears to be sufficient for small or moderate-sized (less than 6 cm) disease. At the University of Florida, this dose resulted in an in-field recurrence rate of 7%.[136] There is no clear evidence of increased local control with doses greater than 3000 cGy.[41,51,126,136] The complication rate, however, clearly increases with higher daily and total doses.[21,24]

The treatment choice in each patient depends on a variety of factors, including the presence or absence of systemic symptoms, histologic subtype, number of anatomic sites involved, anatomic distribution, tumor size, the patient's age, overall medical condition, the potential toxicities of various treatment choices, as well as prior therapy. *It is highly recommended that each patient's primary therapy be decided by collaboration between a radiation oncologist and the medical oncologist or hematologist.* A more extensive discussion of the subtleties of treatment decisions is available in several texts.[27,66,94,100]

Non-Hodgkin's Lymphomas

Selection of Treatment

Compared with Hodgkin's disease, non-Hodgkin's lymphomas present a much more diverse treatment challenge, and routine treatment guidelines do not exist. The treatment must be tailored to each patient. In general, the treatment of non-Hodgkin's lymphoma is divided into treatment for the "favorable" or low-grade lymphomas expected to have an indolent course and the "unfavorable" or intermediate and high-grade lymphomas expected to have an aggressive course. The favorable lymphomas in the Rappaport classification include the nodular lymphomas and diffuse well-differentiated lymphocytic lymphomas; this corresponds to "low-grade" lymphomas in the Working Formulation, except for follicular large-cell lymphomas, which are considered to be "intermediate grade." The unfavorable histologic subtypes include all other lymphomas and correspond to the "intermediate" and "high-grade" lymphomas of the Working Formulation. The treatment modalities for non-Hodgkin's lymphomas include radiation therapy, chemotherapy, occasionally surgery for a localized extranodal primary, or a combination of these modalities.

FAVORABLE HISTOLOGIC FINDINGS. There is no evidence that single-agent chemotherapy, combination chemotherapy, or high-dose chemotherapy with bone marrow transplantation is curative for low-grade lymphomas, although response rates are high. Long disease-free intervals and possible cures may be obtained, however, with moderate-dose radiation therapy in both early and moderately advanced stages of disease.[25,47,93,107,108] Combinations of chemotherapy and radiation therapy have not proved as yet to increase the overall survival rate in patients with the favorable non-Hodgkin's lymphomas.[138] Therefore, the treatment of choice for patients with stages I through III low-grade lymphomas is radiation therapy.

For patients with laparotomy who have stage I or localized stage II disease, it is unclear whether involved-field or comprehensive lymphatic irradiation (Wal-

deyer's ring, mantle, whole abdomen, and pelvic treatment) gives better cure rates.[107] For patients with clinically staged disease, comprehensive lymphatic irradiation appears to be the best option if cure is the goal of treatment since there is a high rate of mesenteric node involvement and subsequent abdominal failure, even if CT scans and lymphangiography have been negative. Patients with stage I and localized stage II extranodal presentations usually have radiation therapy to an extended field to include next-echelon nodal regions. Certain sites, such as the orbit, are less likely to have regional lymph node involvement and thus are usually managed with only involved-field radiation therapy unless clinically involved nodes are present.

In patients with extensive stage II disease with numerous nodal sites involved or stage III disease, the only potentially curative treatment is comprehensive lymphatic irradiation.[25,43,93,108] A few selected stage IV patients with only focal marrow involvement appear to have obtained long disease-free intervals from this approach as well. The dose required for local control in the favorable non-Hodgkin's lymphomas is 2500 to 3000 cGy at 150 to 170 cGy per fraction.

For patients with extensive stage IV disease or those in poor medical condition in whom a curative attempt with prolonged irradiation is not warranted, palliation may be achieved with low-dose total-body irradiation, single-agent chemotherapy, or combination chemotherapy.[10,15,20,55,83,95,123] Observation is a valid option for the asymptomatic patient.[56]

UNFAVORABLE HISTOLOGIC FINDINGS. The majority of early-stage lymphomas with unfavorable histologic findings are treated with combination chemotherapy and radiation therapy to the involved site since results with combined-modality therapy appear to be better than with radiation therapy alone.[58,59,63,78,80,88,101,112] Patients who have small-volume (less than 2.5 cm) stage IA or localized stage IIA disease may be considered for radiation therapy alone with an expected cure rate of about 75%.[50,118,132] Patients with extensive stage II disease, and, in some series, all patients with clinical stage I and II disease, have a high relapse rate after radiation therapy alone, with cure rates ranging from 25% to 50%.[50,118,132] The role of consolidative irradiation after combination chemotherapy is being investigated by the Eastern Cooperative Oncology Group, but retrospective studies suggest that the majority of patients will benefit from both radiation therapy and chemotherapy.[63,78] The dose required for local control in disease with unfavorable histologic findings is unclear. Some data suggest that doses of 4000 cGy or more are optimal.[14] When irradiation is used alone at the University of Florida, doses of 4500 to 5500 cGy are given in 180-cGy daily fractions. When radiation is used after chemotherapy, doses of 3000 to 4000 cGy have been used at the University of Florida and elsewhere[63] with excellent local control. Patients with stage III or IV non-Hodgkin's lymphomas with unfavorable histologic findings are treated with combination chemotherapy as a primary treatment, with or without radiation therapy to sites of original involvement. The most widely used combination chemotherapy program consists of cyclophosphamide, doxorubicin, vincristine, and prednisone (known as "CHOP" chemotherapy).[32] Other chemotherapy regimens use variations of dose or drug scheduling and additional agents (COMA,[133] CHOP-bleo,[120] m-BACOD,[128] PROMACE-MOPP,[38] PROMACE-cytaBOM,[38] MACOP-B[69]). Some of the more recently developed regimens deliver drugs at relatively higher dose intensities, which may affect prognosis.[57]

Radiation Therapy Technique

The treatment fields used in radiation therapy for extranodal non-Hodgkin's lymphoma differ, depending on sites of involvement and on whether radiation therapy is the only treatment or is used for consolidation after chemotherapy. For patients with favorable or unfavorable lymphomas of Waldeyer's ring or cervical lymph nodes who will be treated with radiation therapy alone, fields are comprehensive, covering the nasopharynx, base of tongue, tonsillar fossae and the internal jugular, spinal accessory, submental, preauricular and postauricular, and occipital lymph nodes, as shown in Figures 34-1*C* and 34-1*D*. For patients with lymphomas in Waldeyer's ring having unfavorable histologic findings who have a complete response to chemotherapy, the fields may be confined to sites of the original primary and nodal involvement, as shown in Figure 34-1*E*. If the tumor response to chemotherapy is incomplete or pretherapy imaging is suboptimal, however, the field should be comprehensive, including all areas of original involvement as well as all structures in Waldeyer's ring and all adjacent nodal areas, as in Figures 34-1*C* and 34-1*D*. The Waldeyer's ring field is individualized in each patient and may be modified to accommodate palate lesions or extensive adenopathy involving parotid, preauricular, or occipital nodes.

Parotid gland lesions not associated with extensive neck disease may be treated with an ipsilateral parotid and neck field using electrons and photons (see Fig. 34-2). Intraoral shielding is used to decrease contralateral parotid gland doses, as shown in Chapter 27.

Low-grade lymphomas confined to the lid or conjunctiva may be treated with local fields with 1- to 2-cm margins using electrons or orthovoltage x-ray, as shown in Figures 34-4. Intraorbital lesions are treated with ipsilateral anterior and lateral fields using photons, as shown in Figure 34-5. Extensive orbital lesions require a larger two-field technique.

Lesions limited to the lacrimal gland may be treated with orthovoltage x-ray. If the lacrimal gland lesion extends into the orbit, nasal cavity, or ethmoid sinus, it should be treated with fields similar to those used for a nasal cavity or paranasal sinus lesion. Nasal cavity and paranasal sinus lesions are treated with a three-field technique, as shown in Figure 34-6.

Lesions in the canine fossa are treated with anterior and lateral fields. The course of the infraorbital nerve is included in the field.

Thyroid lymphomas are treated with anterior and posterior fields, weighted in favor of the anterior. Attention must be paid to the inferior border of the field as the lesions may extend into the mediastinum. Laryngeal shielding should be avoided at least for the initial part of therapy to prevent potential shielding of the tumor.

Treatment of Recurrence

Treatment of patients with recurrent disease is dependent on the histology of the recurrence and on the previous chemotherapy and radiation therapy. Patients with favorable histologic features in whom treatment

fails can be treated with radiation therapy for a localized recurrence and single-drug or combination chemotherapy for systemic recurrence. If the patient is asymptomatic, then follow-up without treatment until symptoms develop may be indicated. Occasionally, patients with an initially favorable non-Hodgkin's lymphoma will develop recurrence with transformation into an unfavorable histologic subtype. These patients should be treated aggressively for their unfavorable lymphoma. The reverse situation also occurs wherein a patient initially treated with aggressive chemotherapy for an unfavorable lymphoma relapses with a low-grade lymphoma. These patients are usually observed until development of symptoms and then treated with radiation therapy, single-agent chemotherapy, or a second course of combination chemotherapy. Patients with unfavorable histologic findings who have recurrence with the same disease require aggressive treatment. If radiation therapy was employed initially, an aggressive combination chemotherapy program should be used. Patients who have a relapse after aggressive combination chemotherapy often respond poorly to any further treatment, but can be considered for alternative drug combinations or radiation therapy. The likelihood of cure, however, is remote. The role of high-dose chemotherapy with bone marrow transplantation in this setting is being evaluated by several groups.[110,121,135]

RESULTS OF TREATMENT

Hodgkin's Disease

The 10-year cause-specific and absolute survival rates for 153 patients with stage I and II supradiaphragmatic Hodgkin's disease treated at the University of Florida between 1964 and 1986 are 84% and 77%. This result is similar to those achieved by the Joint Center for Radiation Therapy in Boston[73] and by Stanford University.[52] Important prognostic indicators for treatment failure in early-stage disease treated with radiation therapy alone include bulky disease, large mediastinal adenopathy, the total number of sites of involvement, and B symptoms.

As the stage of disease increases, survival rates decrease even when more aggressive treatment is used (Table 34-2).[94] Patients with intermediate-stage disease (IIB, or $IIIA_1$ or IIIAS with minimal spleen involvement) have a higher relapse rate when treated with radiation therapy alone compared with combined modality therapy, but their overall survival rate is the same, since many patients can be salvaged with chemotherapy for recurrence of disease after radiation. The survival rate in more advanced stage III and IV disease treated with chemotherapy alone is about 50%.[79] The sites of failure after chemotherapy alone are sites of previous nodal disease in the majority of cases.[146] Preliminary studies of combined modality therapy for stage III and IV disease with MOPP or ABVD plus radiation therapy show continuously disease-free survival rates of 60% to 80%.[7,11,114,122]

Non-Hodgkin's Lymphomas

Favorable Histologic Findings

Radiation therapy is curative in 50% to 90% of patients with stage I and localized stage II lymphomas with favorable histologic findings (Table 34-3), depending on patient selection and extent of staging. Most failures after radiation therapy are outside the radiation field. In certain sites, such as the orbit, local failures are rare, with multiple series reporting 100% local control in lesions with both favorable and unfavorable histologic features.[40,117] Patients whose disease has been staged with laparotomy have a higher likelihood of cure after limited field irradiation than do patients with clinically staged disease.[107] The relapse-free survival rate of a small group of patients treated at the University of Florida with comprehensive lymphatic irradiation for advanced stage II and III and early-stage IV disease with favorable histologic features was about 60% at 10 years after treatment.[93] These results are similar to those achieved at the Medical College of Wisconsin (Milwaukee) and Stanford University[25,43,108] with similar treatment. The response rates and median duration of survival after low-dose total-body irradiation in advanced stage III and IV non-Hodgkin's lymphoma at the University of Florida (Table 34-4)[95] are similar to those achieved at other institutions and to results achieved with chemotherapy, with or without total-body irradiation,[10,15,20,55,83,123] or observation in selected patients.[56] The treatment approaches for advanced III and IV disease do not appear to be curative.

Unfavorable Histologic Findings

Radiation therapy is curative in 50% to 90% of patients with stage I or localized stage II disease with unfavorable histologic features (Table 34-5), depending on patient selection and extent of staging. In patients with laparotomy-staged small-volume stage IA disease, a 10-year actuarial relapse-free survival rate of 91% has been reported, but results with radiation therapy alone are significantly poorer in patients with non-laparotomy-staged disease.[50] Other investigators report 5-year survival rates of 78% in patients with laparotomy-staged disease with stage I and localized stage II disease versus a 5-year survival rate of 60% in patients with non-surgically-staged disease.[5,74] In the majority of cases, however, combined modality therapy offers the best chance of cure (Table 34-6). In advanced stage non-Hodgkin's lymphomas with unfavorable histologic features, CHOP chemotherapy results in a 25% to 40% 5-year survival rate.[22,32] It is unclear whether the newer chemotherapy regimens will result in better long-term results than the CHOP regimen.[99]

FOLLOW-UP POLICY

Patients with both Hodgkin's and non-Hodgkin's lymphomas should have close follow-up, especially within the first 3 years. About 80% of relapses in patients treated for Hodgkin's disease will be detected in the first 3 years, but relapses continue to occur for 12 years. Relapses in patients with non-Hodgkin's lymphomas with unfavorable histologic features usually occur within the first 2 years, and those in patients with lymphomas with favorable histologic features usually occur within 5 to 6 years. Late recurrence is not rare.

The follow-up examination should include a physical examination, periodic blood tests (including complete blood cell counts, platelet count, erythrocyte sedimentation rate, and thyroid function studies), and periodic chest roentgenography.

TABLE 34-2. Hodgkin's Disease: Treatment Recommendations and Results Achieved at the University of Florida

Stage	Treatment	10-Year Survival Rate* (%)		
		Relapse-free	Absolute	Cause-Specific
Low-risk				
IA, IB, IIA, IIB—no poor prognostic factors	MTNI or TNI	90	82	93
Intermediate-risk				
IA, IB, IIA, IIB—large mediastinal mass or more than four sites involved	MTNI or TNI	60	86	83
	CB	80	78	78
$IIIA_1$	TNI	80	80	80
$IIIA_{1S}$—minimal	TNI	50	90	80
	CB	100	75	75
High-risk				
$IIIA_{1S}$—extensive	CB	67	63	60
IIIB	CB	40	40	40
IV	CH	20	29	32
III, IV†	alt. CB or alt. CH	67–85	77–100	No data

MTNI, modified total nodal irradiation; TNI, total nodal irradiation; CB, combined modality with radiation therapy and chemotherapy; CH, chemotherapy alone; alt. CB, chemotherapy alternating with segments of irradiation; alt. CH, alternating chemotherapy regimens.

* In relapse-free survival, only disease relapse was counted as an event. For absolute survival, death from any cause was counted as an event. For cause-specific survival, deaths due to Hodgkin's disease or treatment-related causes (ie, complications of treatment or secondary leukemia) were counted as events.

† Three-year results from Stanford University trials.[122]

(Mendenhall NP, Million RR. Hodgkin's disease: Radiation therapy. In Rakel RE, ed. Conn's Current Therapy 1990. Philadelphia, WB Saunders, 1990:362)

TABLE 34-3. Results in Patients With Early-Stage, Favorable-Histology, Non-Hodgkin's Lymphoma Treated With Radiation Therapy Alone

	Patients	Stage	5-Year Relapse-Free Survival
Stanford University[107]	88	CS I and II	50%
	36	PS I and II	86%
University of Florida*	19	CS I and II	67%
Princess Margaret Hospital[47]	218	CS I and II	73%

CS, clinically staged without laparotomy; PS, pathologically staged with laparotomy.

* University of Florida data: patients treated between September 1964 and October 1987; analysis October 1988 by Robert J. Amdur, MD.

TABLE 34-4. Response Rates to Total Body Irradiation in Previously Untreated Lymphomas

Histology (No. Patients)	Complete Response	Partial Response	Total Complete Response + Partial Response/ No. Treated	Median Duration of Response in Complete Responders (Years)	Median Time to Progression in Partial Responders (Months)
Favorable (27)	20	6	26/27	3.8	10.5
Unfavorable (17)	6	11	17/17	2.5	7.0

CR, complete response; PR, partial response.

(Modified from Mendenhall NP, Noyes WD, Million RR. Total body irradiation for stage II-IV non-Hodgkin's lymphoma: 10-year follow-up. J Clin Oncol 1989;7:70)

TABLE 34-5. Results in Patients With Early-Stage, Unfavorable-Histology, Non-Hodgkin's Lymphoma Treated With Radiation Therapy Alone

	Patients	Stage	5-Year Relapse-Free Survival
Stanford University[58]	34	I	48%
	40	II	35%
Joint Center for Radiation Therapy[88]	17	I and II	52%
University of Florida*	32	I	61%
	17	II	44%
Chicago[50]	22	I	91%
	14	II	35%

* Head and neck sites only. University of Florida data; patients treated between September 1964 and October 1987; analysis October 1988 by Robert J. Amdur, MD.

COMPLICATIONS OF TREATMENT

Radiation Therapy

Radiation therapy to a Waldeyer's ring field will usually result in moderate transient xerostomia. With a total dose of 2500 to 3000 cGy, younger patients will frequently recover good salivary function. Doses above 5000 cGy usually result in persistent xerostomia that is moderate to severe in most patients. Older patients may develop permanent xerostomia after doses less than 5000 cGy. All patients who are undergoing oral irradiation should have careful instruction in dental hygiene, and those receiving doses above 3000 cGy should have a dental evaluation before or during treatment. Daily fluoride applications are recommended even if xerostomia resolves (see Chap. 10).

Irradiation to other sites in the head and neck, including the orbit, may include the eye as part of the treatment volume for lymphoma. With doses below 5000 cGy, good vision is almost always maintained.[40,106,117] A cataract may develop, but the cataract can be surgically removed with the same results as removal of cataracts from nonirradiated patients.

Patients irradiated in the neck region are also at risk for hypothyroidism. This is an easily managed complication, and routine thyroid examination with thyroxine and thyrotropin determinations at yearly intervals is recommended for detection and treatment of hypothyroidism before it is clinically manifest.

Patients irradiated to the neck may also experience Lhermitte's sign 4 to 6 weeks after radiation therapy. This is a transient syndrome that may last several months and consists of an electric shock–like sensation down the spinal cord on flexion of the neck. If the symptoms are disturbing, a soft cervical collar can be worn for 4 to 6 weeks.

Patients successfully treated for Hodgkin's disease may have an increased risk of subsequent solid malignancy in or out of the previous radiation treatment portals.[96]

Chemotherapy

Acute complications of chemotherapy include nausea and vomiting, alopecia, and pancytopenia with resultant risks of infection. A moderate to severe transient mucositis of the oral cavity can be seen with the use of some chemotherapeutic agents, such as methotrexate, 5-fluorouracil, and doxorubicin.[18,19] Long-term complications include the possibility of prednisone-induced bilat-

TABLE 34-6. Results in Patients With Early-Stage, Unfavorable-Histology, Non-Hodgkin's Lymphoma Treated With Combined-Modality Therapy

	Patients	Stage* <10 cm	5-Year Relapse-Free Survival
Stanford University[58]	23	I	78%
	71	II	70%
Joint Center for Radiation Therapy[88]	23	I and II†	81%
University of Florida*	16	I and II	47%
Arizona and Vancouver[63]	142	I and II	82%
National Cancer Institute[80]	47	I	96%

* Tumors >10 cm not included.

† The majority of patients in series were clinically staged.

eral femoral head necrosis, vincristine neuropathy, bleomycin-induced pneumonitis or pulmonary fibrosis,[23] cardiotoxicity due to doxorubicin, cyclophosphamide-induced hemorrhagic cystitis, and alkylating agent–induced sterility (particularly in males)[142] and leukemia.[140] The risk of acute leukemia after MOPP chemotherapy is about 7%; this risk does not seem to increase significantly with the addition of irradiation or the use of chemotherapy in the salvage setting rather than the primary setting.[64,96]

Combined Modality Treatment

The complications of combined modality treatment include all of the above, plus a probable increased risk for complications that occur with both treatments, such as second solid malignancies, cardiac disease in patients treated with both mediastinal irradiation and doxorubicin, and pulmonary disease in patients treated with both lung irradiation and bleomycin.

MYCOSIS FUNGOIDES

Mycosis fungoides is a malignant disorder of T lymphocytes that have a special affinity for the epidermis. The disease often presents as a rash. This may slowly change to irregularly shaped, slightly indurated plaques. The plaques evolve into nodular skin tumors (Fig. 34-9), and eventually there is involvement of the lymph nodes and internal organs. The natural history of mycosis fungoides is variable, and the course may be prolonged, irrespective of therapy.

Patients with mycosis fungoides rarely have oral manifestations. Sites of presentation include the tongue (most common), soft palate, hard palate, tonsils, and epiglottis. Oral lesions are most frequently seen in later stages of the disease. Clinically, the oral lesions are similar to skin lesions beginning as erythematous patches and progressing to ulcerated plaques.[35]

Figure 34-9. Mycosis fungoides involving the skin of the right forehead.

Staging

Staging of mycosis fungoides includes assessment of skin involvement, including size, distribution, thickness, and pigmentary changes of all lesions on the body. An examination of the nodal regions is also necessary, with biopsy of enlarged, suspicious nodes. All patients should have a chest roentgenogram, liver function study, complete blood cell count, and, in advanced stage patients, a bone marrow biopsy. A staging system has been proposed for mycosis fungoides.[13]

Treatment

When mycosis fungoides is limited to the skin, treatment can be electron-beam irradiation, topical applications of chemotherapy, or photochemotherapy with psoralens and ultraviolet light (PUVA). In the later stages, with nodal or internal organ involvement, treatment often consists of combination chemotherapy. There appears to be no difference in ultimate survival rates, regardless of which approach is taken first.[67]

In the early stages, with localization to the skin, it is possible to have prolonged remissions and possible cures with electron-beam irradiation. In the Stanford experience, about 40% of the patients with limited plaque disease were continuously free of disease for 8 to 10 years. When the disease has spread to extracutaneous sites, cure is rare and therapy is primarily palliative.[98]

PEDIATRIC LYMPHOMAS

Hodgkin's Disease

A higher proportion of pediatric patients have lymphocyte-predominant histology and a lower proportion have lymphocyte-depleted histology than in the adult population. There is no difference between the natural history of Hodgkin's disease in the pediatric and adult populations. Stage for stage, the relapse-free survival and cure rates in major treatment centers are as good as, or better than, those obtained in adult Hodgkin's disease.

A major difference between pediatric and adult patients, however, is the musculoskeletal hypoplasia observed when doses greater than 2000 cGy are delivered to preadolescent children. Because of the significant complications of irradiation, chemotherapy plays a much more prominent role in the management of early-stage disease in young children.[28,29,60] Radiation therapy, when given to preadolescent children, is usually modified to treat lesser volumes of tissue with lower doses than in adult patients. A report from Stanford University suggests that excellent cure rates with a marked decrease in musculoskeletal abnormalities can be achieved with combined modality therapy using six courses of MOPP chemotherapy and involved field radiotherapy with doses tailored to the age of the patient. Doses of 1500 cGy were used for children with a bone age less than 5 years,

2000 cGy for bone ages between 6 and 10 years, and 2500 cGy for bone ages between 11 and 14 years. The leukemia incidence reported in this group of patients was similar to that observed in adult series treated with MOPP alone.[29]

Non-Hodgkin's Lymphomas

Childhood non-Hodgkin's lymphomas are different in some important respects from adult non-Hodgkin's lymphomas. Rappaport's classification, with its proven relevance in adults, is less useful in the pediatric age group. Histologically, childhood non-Hodgkin's lymphomas are almost always diffuse high-grade malignancies. There is a much greater predilection for evolution to acute leukemia and a higher frequency of involvement of the central nervous system. Generally, childhood non-Hodgkin's lymphoma can be grouped under three main headings: (1) lymphoblastic, (2) histiocytic, and (3) Burkitt's lymphoma. Diffuse histiocytic lymphoma in the pediatric population is similar to its presentation in adults. Lymphoblastic lymphomas typically present as a supradiaphragmatic tumor, often in the mediastinum in adolescent males. There is a marked propensity for leukemic evolution and involvement of the central nervous system. The classic description of Burkitt's lymphoma was made by Burkitt in his study of African patients, and excellent subsequent reviews are available.[147] It is a predominantly extranodal tumor, mainly affecting the mandible and, less commonly, the abdominal viscera. This lymphoma has a unique geographic distribution in Africa and has an association with Epstein-Barr virus. Kinetic studies of Burkitt's lymphoma cells have revealed a doubling time of about 24 hours, making this one of the fastest-growing human tumors. The proliferative potential of Burkitt's lymphoma is clinically apparent, with many of these tumors reaching massive sizes within days or weeks.

After its original description in Africa, a number of cases of "Burkitt-like" tumors were recognized in other parts of the world. In African patients the mean age is 7 with a range of 2 to 16 years of age; the male-to-female ratio is 2 : 1. In American patients the mean age is 11, with a range of 2 to 27 years of age. The majority of American patients have intraabdominal tumors, apparently arising from Peyer's patches or mesenteric lymph nodes. The most frequent clinical presentation is intestinal obstruction or an abdominal mass. Other areas of intraabdominal involvement include the ovaries, kidneys, or retroperitoneum. A few patients have enlarged cervical nodes.

Staging

The Ann Arbor staging system is much less useful for pediatric tumors than for tumors in adults because of the tendency in childhood lymphomas for widespread dissemination and frequent bone marrow or central nervous system involvement. Other staging systems have been proposed specifically for the pediatric non-Hodgkin's lymphomas.[137] The staging work-up of childhood lymphomas is abbreviated because of the aggressive, rapid growth potential and the need for systemic therapy in all patients. Staging requires a history and physical examination, complete blood cell count, renal and hepatic function tests, chest roentgenogram, skeletal survey or bone scan, bone marrow aspiration and biopsies, and lumbar puncture. Additional studies such as CT scan of the abdomen, ultrasound, barium studies of the gastrointestinal tract, and either MRI of the spine or myelography may be done in selected patients.

Treatment

The principles of treatment useful for adults with non-Hodgkin's lymphomas are not applicable to children. In childhood non-Hodgkin's lymphomas, the primary treatment is combination chemotherapy. Most of the regimens use a combination of cyclophosphamide, methotrexate, doxorubicin, vincristine, and prednisone. With combinations of these drugs, 80% to 90% of children are able to achieve a complete response. Consolidative irradiation to involved sites has been demonstrated to be unnecessary in nonosseous primary pediatric lymphomas.[77] In advanced-stage disease, irradiation is used in the elective treatment of the central nervous system because of the lower chemotherapy drug levels that reach the central nervous system because of the blood–brain barrier. There is a high risk for lymphomatous involvement of the central nervous system in all patients with primary lesions of the head and neck and mediastinum and in those with massive abdominal disease or bone marrow involvement. Without elective treatment, central nervous system disease develops in about 30% of childhood cases at high risk and the outcome is usually fatal. Intrathecal drugs are used for central nervous system prophylaxis; cranial irradiation may be recommended if the central nervous system is known to be grossly involved at diagnosis.

Results of Treatment

The survival rate in patients with localized disease (stages I and II) is good, approaching 70% to 90%. In patients with more advanced disease, the prognosis is much poorer, with reports of 2-year survival rates of 10% to 30%.[103]

PLASMACYTOMA

Solitary plasmacytoma of the bone and soft tissue is a rare neoplasm that can involve the head and neck region. The incidence is about 3 per 100,000 population, with a median age of presentation of 60 years. In one series the age ranged from 28 to 74, with the majority of patients in the sixth, seventh, and eighth decades of life.[92] There is a male-to-female ratio of 4 : 1. Tumors can be categorized into two groups: osseous and nonosseous (extramedullary) primary lesions. About 80% of the extramedullary plasmacytomas occur in the head and neck, most notably in the upper air passages. The nasal vestibule, maxillary sinus, nasopharynx, tonsil, and trachea are the more common sites of presentation. Other sites include the orbit, thyroid, skin, and gingiva.[65] The tumors are usually submucosal masses. The regional cervical lymph nodes may be involved in 10% to 25% of cases, and an occasional patient has lymph node disease and no obvious primary site. In 30% to 40% of patients, the disease progresses to multiple myeloma on long-term follow-up. The incidence of progression to multiple myeloma is higher in patients with a bone lesion as compared with an extramedullary lesion.

The recommended work-up includes a bone marrow biopsy, skeletal survey or bone scan, urine study for Bence-Jones protein or quantitative determination of κ and λ light chains, serum protein electrophoresis and immunoelectrophoresis, serum calcium and uric acid levels, complete blood cell count, and renal function studies.

The treatment for solitary plasmacytoma is localized radiation therapy. An analysis of the dose required for local control showed that a dose of 3500 to 4000 cGy over 4 to 5 weeks was sufficient for local control in 94% of patients.[92] There was no obvious difference in the dose required for osseous versus extramedullary lesions.

The survival rate in a group of 15 patients was 87% at 5 years. In 5 of the patients the disease progressed to multiple myeloma but had an indolent course. Chemotherapy is used for generalized relapse. Solitary new plasmacytomas may occur and should be treated with radiation therapy in the same manner as a primary lesion.

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35

COST OF MANAGEMENT OF HEAD AND NECK CANCER

RODNEY R. MILLION AND MARGUERITE C. SIGAL

In this chapter several examples are given of the costs involved in the management of head and neck cancer. The examples in Tables 35-1 through 35-9 represent costs incurred by specific patients treated in Gainesville, Florida, and therefore do not represent average costs based on an analysis of large numbers of patients. They should be considered to be representative of uncomplicated treatment costs; if the patient develops a complication, which is all too frequent, then the cost escalates quite rapidly. The patient often has substantial indirect costs from loss of salary, travel, and housing that are equal to the professional and hospital charges.

Thawley and Ogura wrote a review on the direct cost of laryngeal surgery.[4] The costs that they quoted were for the year 1978. Suen and associates reviewed the direct and indirect costs for five head and neck cancer cases treated in Little Rock, Arkansas, during the late 1970s.[3] This is the only article that included the indirect costs of salary loss and so forth. Miller and associates reviewed the cost of microsurgical reconstruction for 17 malignant head and neck tumors and found an average direct cost of $37,400 with 21 days of hospitalization. Indirect costs were not included. They concluded that the benefits were worth the cost.[1] Mittal and associates compared the costs of hemilaryngectomy and irradiation for early glottic carcinomas (T1N0) managed at Washington University, St. Louis, Missouri, for the years 1980 and 1981 (Tables 35-10 and 35-11).[2] For current surgical admissions at the University of Florida, the semiprivate hospital room represents 25% to 30% of the cost; the surgeon's fee, 15% to 20%; the anesthetist's fee, 15% to 20%; and the use of the operating room and recovery room, 10% to 20%.

The cost of radiation therapy escalated rapidly in the past decade owing to the expensive treatment equipment, more frequent use of computerized dosimetry, the use of specialized blocking techniques such as blocks made of Lipowitz's metal, and the increased use and costs of physicists, dosimetrists, and radiation therapy technologists to assist in the overall management of the patient. While these various factors have improved the sophistication and quality of delivery of radiation therapy, there has not been a corresponding increase in cures per dollar spent. Most insurance carriers reimburse the patient for outpatient radiation therapy.

The cost of multiagent chemotherapy regimens that include cisplatin and bleomycin can be quite expensive, particularly if the patient is hospitalized for part of the treatment or for complications of treatment. Unfortunately, insurance carriers still do not always reimburse for chemotherapy treatments, and the patient is often left to pay this bill out of pocket.

The costs indicated in Tables 35-1 through 35-9 are substantial, and one could rapidly see a total bill on the order of $30,000 to $35,000 if the patient had four cycles of cisplatin and bleomycin, 5 weeks of radiation therapy, and a major operative procedure. Residency training programs are remiss in not familiarizing young physicians with the costs their patients are incurring. The physician must constantly think in terms of the benefit-to-cost ratio.

The American Cancer Society is frequently instrumental in assisting patients with nonmedical expenses such as room, board, travel, and noncancer drugs. Many patients must leave home, particularly for radiation therapy or chemotherapy, and the added costs of day-to-day living are not paid by insurance. It is in this area that the American Cancer Society (especially in Florida) has been so generous in assisting patients.

TABLE 35-1. Radiation Therapy Costs for Carcinoma of the Vocal Cord*

	1980	1989
Professional fee†	$1900	$3379
Hospital fee	1450	2531
Travel	300	300
TOTAL	$3650	$6210

* Cobalt-60, 28 treatments.
† Includes cost of physics support.

TABLE 35-2. Radiation Costs for Carcinoma of the Nasal Vestibule, Including an Interstitial Implant After External-Beam Radiotherapy

	Cost (1989)
Professional fees	
Radiation oncologist—external-beam therapy, including physics support	$ 3225
Radiation oncologist—interstitial implant, including physics support	2888
Anesthesiologist, pathologist, and cardiologist—for interstitial implant	484
Subtotal	$ 6597
Hospital fees	
External-beam therapy, including physics support	3104
Interstitial implant (5-day admission)	3333
Subtotal	$ 6437
TOTAL	$13034

TABLE 35-3. Radiation Therapy Costs for Carcinoma of the Tonsil*

	1980	1989
Professional fee†	$2800	$ 7395
Hospital fee	2700	7727
Travel	400	400
TOTAL	$5900	$15,522

* Cobalt-60, treatments given twice a day.
† Includes cost of physics support.

TABLE 35-4. Surgical Costs for Direct Laryngoscopy

	1980	1989
Professional fees		
Surgeon	$ 240	$ 609
Anesthesiologist	250	384
Pathologist	207	180
Cardiologist	35	53
Radiologist	14	27
Subtotal	$ 746	$1253
Hospital fees		
2-day hospitalization (including 1 hour of operating room time)	$ 870	$3950
TOTAL	$1616	$5203

TABLE 35-5. Surgical Costs for Laryngectomy and Radical Neck Dissection

	1980	1989
Professional fees		
Surgeon*	$2330	$ 4960
Anesthesiologist	2163	1795
Pathologist (laboratory)	375	425
Radiologist	95	135
Pathologist (surgical)	60	486
Subtotal	$5023	$ 7801
Hospital fees		
17-day admission (including operating room time)	$4939	$12,787
TOTAL	$9962	$20,588

* Laryngectomy without radical neck dissection cost $1375 in 1980, $3621 in 1989.

TABLE 35-6. Surgical Costs for Hemimandibulectomy and Radical Neck Dissection

	1980	1989
Professional fees		
Surgeon	$ 3500	$ 5900
Anesthesiologist	1200	3780
Pathologist (blood, laboratary, surgical pathology)	665	875
Radiologist	80	135
Cardiologist	70	106
Subtotal	$ 5515	$10,796
Hospital fees		
17-day admission (including operating room time)	$ 8554	$17,396
TOTAL	$14,069	$28,192

TABLE 35-7. Surgical Costs for Superficial Lobe Parotidectomy

	1980	1989
Professional fees		
Surgeon	$ 920	$ 2450
Anesthesiologist	603	1600
Pathalogist	270	450
Radiologist	20	54
Cardiologist	35	53
Subtotal	$1848	$ 4607
Hospital fees (6-day admission)		
Semiprivate room (6 days)	$ 738	$ 1500
Electrocardiogram ×2	48	124
Blood bank	85	150
Chest roentgenogram	24	60
Recovery room	140	367
Operating room	805	4500
Laboratory	82	52
Surgical pathology	35	106
Pharmacy	226	288
Surgical supplies	77	1502
Anesthesia supplies	195	1038
Subtotal	$2455	$ 9687
TOTAL	$4303	$14,294

TABLE 35-8. Costs for Diagnostic Radiologic Procedures

	1980	1989
CT scan of larynx		
Without contrast	$360	$580
With contrast	$465	$705
CT scan of paranasal sinuses		
Without contrast	$360	$580
With contrast	$465	$647
MRI of nasopharynx		
Without contrast	—	$720
With contrast	—	$876

TABLE 35-9. Chemotherapy Costs

	1980	1989
Single-agent chemotherapy (outpatient treatment)		
Consultation	$ 110	$ 170
Methotrexate: eight doses × 70 mg each	248	242
Office visits × 8	216	384
Chest roentgenograms × 5	160	200
Complete blood cell counts × 12	144	240
SMA15 × 3		
To interpret	38	50
To draw	12	27
Administration of chemotherapy drugs × eight doses	120	800
Subtotal	$1048	$2113
Hospitalization for leukopenia (5 days)	$1754	$5500
Professional fee for hospitalization	245	425
Total	$3047	$8038
Multiagent chemotherapy (outpatient treatment)		
Cisplatin: 150 mg IV	$ 506	$ 445
Bleomycin: 15 units × 5 doses	1022	1032
Office visits	27	48
Complete blood cell count	12	23
Administration of chemotherapy drugs	23	230
Creatinine clearance	23	62
Total per course	$1613	$1840
Total for four courses	$6452	$7360

TABLE 35-10. Average Cost of Radiation Therapy for Early Vocal Cord Carcinoma (1980–1981)

Number of Patients Treated	Average Radiation Therapy Cost per Patient	Transportation Cost per Patient for Entire Treatment Course	Totol Cost per Patient for Entire Course of Treatment
1980—8	$3013*	$112	$3125
1981—10	$2433	$283†	$2716
Total—18	$2723	$197	$2920

* 1 patient received entire radiation treatment as inpatient. His total expenses were $9,075.

† 1 patient rented an apartment next to the hospital. His total expenses were $980.

(Mittal B, Rao DV, Marks JE, Ogura JH. Comparative cost analysis of hemilaryngectomy and irradiation for early glottic carcinoma. Int J Radiat Oncol Biol Phys 1983;9:408)

TABLE 35-11. Average Cost of Hemilaryngectomy and Average Hospital Stay for Each Patient (1980–1981)

Number of Patients Treated	Surgeon's Fee* per Patient	Hospitalization Cost† per Patient	Total Cost per Patient	Days in the Hospital† per Patient
1980—8	$1546	$4341	$5887	13
1981—7	$1595	$5347	$6942	15
Total—15	$1571	$4844	$6415	14

* Includes 1-year follow-up as an outpatient.

† Hospitalization cost and stay in hospital are counted from the day of hemilaryngectomy.

(Mittal B, Rao DV, Marks JE, Orgura JH. Comparative cost analysis of hemilaryngectomy and irradiation for early glottic carcinoma. Int J Radiat Oncol Biol Phys 1983;9:408)

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